PYRIDOSTIGMINE TO ENHANCE GASTROINTESTINAL RECOVERY AFTER COLORECTAL SURGERY

by

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Discipline of Surgery

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A thesis submitted in 2023 to the University of Adelaide for the degree of Doctor of Philosophy in Surgery.

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CONTENTS

ABSTRACT

Postoperative ileus (POI) refers to the delayed return of gastrointestinal (GI) function and is a common complication following colorectal surgery. POI increases morbidity, mortality, and healthcare costs. The cholinergic anti-inflammatory pathway (CAIP) is crucial in developing POI, but limited preventive strategies target this pathway. This thesis examines acetylcholinesterase inhibitors (ACIs), such as pyridostigmine and neostigmine, as a method to impact the CAIP and improve GI recovery, culminating in a novel randomised controlled trial (RCT).

This thesis comprises seven papers, beginning with a comprehensive literature review summarising the current applications of ACIs in abdominal surgery, including neuromuscular reversal during anaesthesia, resolving acute colonic pseudo-obstruction, and POI. A systemic review of RCTs examines ACIs efficacy in improving GI recovery after abdominal surgery, revealing that five of eight studies had a reduction in time to first stool. Despite variations in methodology and bias concerns, the evidence supported using ACIs to improve GI function recovery. However, it emphasises the need for an RCT embedded in a modern enhanced recovery protocol (ERP), especially for colorectal surgery patients. Additionally, in a 335-patient cohort study, neostigmine/glycopyrrolate administration during neuromuscular reversal delayed GI function recovery (GI-2 (validated measure of time to first stool and tolerance of oral diet) median 3 vs. 2 days, p=0.035) without affecting POI rates.

Furthermore, we investigate the financial impact of POI, providing Australian first data for 415 colorectal patients, revealing an increase in total hospital cost by 26.4% (AU$37,690 vs. AU$29,822, p<0.001) due to increased length of stay and complications. Giving a broader perspective, we present the first meta-analysis examining the global financial

burden of POI following abdominal surgery, demonstrating a 66.3% increase (95%CI [34.8-97.9], $p<0.0001$, $I_2=98.4\%$) in total hospital cost. This study estimates POI amounts to a US$4.1 billion burden annually in the USA, underscoring the need to reduce its incidence with adjunctive therapies.

The primary study of this thesis is the first double blinded RCT that evaluates the addition of pyridostigmine to the current ERP following colorectal surgery. With 130 patients, the study shows a significant reduction in time to GI-2 with the addition of pyridostigmine (2 (IQR 1-3) vs. 3 (2-4) days; $p=0.015$), supporting the hypothesis that it improves GI recovery. However, no significant differences were observed in POI, length of hospital stay or 30-day complications.

Furthermore, we employed machine learning techniques to identify new POI risk factors and guide preventative strategies. Using multivariate logistic regression and comparing it to machine learning models, particularly radial basis function, decision trees and multiple layer perceptron (MLP), MLP outperformed the other models and identified sarcopenia as a potentially modifiable risk factor for POI.

This thesis provides novel findings, highlighting the significant financial burden of POI following abdominal surgery. It provides evidence for the efficacy of pyridostigmine in improving GI recovery. These findings contribute to understanding GI recovery and emphasise the importance of targeted prevention strategies to reduce the incidence of POI.

STATEMENT OF ORIGINALITY OF WORK

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

DEDICATION

This thesis is dedicated to my wife, Fe. The last three years represent some of the most challenging years we have faced together, but we have also experienced some of the best times in our lives. As we grew in our marriage, the arrival of our precious baby Lily brought even more joy and love into our family. Fe, your unwavering support, understanding, and sacrifices have been the driving force behind my research. Without you, none of this would have been possible.

Lily, your presence has brought so much happiness and has filled our family with love and joy. I look forward to watching you grow as a proud parent.

To my parents, Neil and Susie, your constant belief in me and care have provided me with an excellent foundation in life. The values of hard work, resilience, and determination that you have instilled in me are inspiring. Every day, you have been a source of encouragement and strength.

To my brother, Will, from our shared childhood to your presence beside me at our wedding, I am grateful for your support and our deep connection. Your presence has always been a reminder of the importance of family and our happiness.

This thesis is a testament to the support and strength that stems from our family.

ACKNOWLEDGEMENTS

I sincerely thank my supervisors, Associate Professor Tarik Sammour and Dr. James Moore. Your guidance, support, and encouragement have been instrumental in completing this research. You have not only provided me with mentorship but have inspired me to strive towards becoming an academic surgeon. With your expertise and assistance, this was possible.

I warmly thank my colleagues, Dr. Sergei Bedrikovetski, Dr. Tracy Fitzsimmons, Associate Professor Hidde Kroon, and Dr. Thuy-My Nguyen. Your company has been a constant source of happiness throughout this research journey. Your insights and contributions have pushed me in my research, and I am grateful for our discussions and experiences.

I would also like to express my appreciation to the colorectal unit, particularly Dr. Mark Lewis, Dr. Michelle Thomas, Associate Professor Ryash Vather and Dr. Matthew Lawrence. Your support and welcoming nature have made my time with the unit thoroughly enjoyable. The assistance I received from each of you has truly enhanced the quality of this research.

Lastly, I would like to thank the nursing staff at the Royal Adelaide Hospital, particularly Ward 5E and ARRC, and St. Andrews Hospital. Your help in conducting my trial and patience in accommodating my endless requests have been appreciated. Your dedication to your patients and willingness to assist researchers are crucial to the success of these studies.

To all those mentioned above, I am genuinely grateful for your assistance, mentorship, and friendship.

PUBLICATIONS INCLUDED IN THIS THESIS.

Traeger L, Kroon HM, Bedrikovetski S, Moore JW, Sammour T. The impact of acetylcholinesterase inhibitors on ileus and gut motility following abdominal surgery: a clinical review. ANZ J Surg. 2022 Jan;92(1-2):69-76. https://doi.org/10.1111/ans.17418

Traeger L, Dudi-Venkata N, Bedrikovetski S, Kroon HM, Moore JW, Sammour T. Use of acetylcholinesterase inhibitors in reducing postoperative ileus following abdominal surgery: A systematic review. Dig Surg. 2023 Dec. https://doi.org/10.1159/000535753

Traeger L, Hall TD, Bedrikovetski S, Kroon HM, Dudi-Venkata NN, Moore JW, Sammour T. Effect of neuromuscular reversal with neostigmine/glycopyrrolate versus sugammadex on postoperative ileus following colorectal surgery. Tech Coloproctol. 2023 Mar;27(3):217-226. https://doi.org/10.1007/s10151-022-02695-w

Traeger L, Koullouros M, Bedrikovetski S, Kroon HM, Thomas ML, Moore JW, Sammour T. Cost of postoperative ileus following colorectal surgery: A cost analysis in the Australian public hospital setting. Colorectal Dis. 2022 Nov;24(11):1416-1426. https://doi.org/10.1111/codi.16235

Traeger L, Koullouros M, Bedrikovetski S, Kroon H, Moore J, Sammour T. The global cost of postoperative ileus following abdominal surgery: meta-analysis. BJS Open. 2023 June;7(3) https://doi.org/10.1093/bjsopen/zrad054

CHAPTERS INCLUDED IN THIS THESIS UNDER REVIEW.

Traeger L, Bedrikovetski S, Fitzsimmons T, Nguyen TM, Moore JW, Lewis M, Sammour T. Pyridostigmine to Reduce the duration of postoperative Ileus after Colorectal Surgery – a double blinded Randomised Controlled Trial. [Chapter 7]

Traeger L, Bedrikovetski S, Hanna J, Moore J, Sammour T. Machine learning prediction model for postoperative ileus following colorectal surgery. [Chapter 8]

LIST OF ABSTRACTS AND PRESENTATIONS

ORAL PRESENTATIONS

Traeger L. Sarcopenia in Colorectal Surgical Patients. Royal Adelaide Hospital & Queen Elizabeth Hospital, 2023, Departmental Research Meeting, Adelaide, Australia.

Traeger L, Hall T. Effect of neuromuscular reversal with neostigmine/glycopyrrolate versus sugammadex on postoperative ileus following colorectal surgery. Central Adelaide Local Health Network, 2023, Anaesthetic Departmental meeting, Adelaide, Australia.

Traeger L, Bedrikovetski S, Nguyen TM, Lewis M, Moore JW, Sammour T. Pyridostigmine to reduce the duration of postoperative ileus after colorectal surgery – a double blinded randomised controlled trial. Royal Australasian College of Surgeons (RACS), 2023, Annual Scientific Congress (ASC), Adelaide, Australia.

Traeger L, Bedrikovetski S, Nguyen TM, Lewis M, Moore JW, Sammour T. Pyridostigmine to reduce the duration of postoperative ileus after colorectal surgery – a double blinded randomised controlled trial. University of Adelaide, 2023, 17th Annual Florey Postgraduate Research Conference, Adelaide, Australia.

Traeger L. Accelerating Gastrointestinal Recovery: The Power of Pyridostigmine, University of Adelaide, 2023, 3 Minute Thesis Final, Adelaide, Australia.

Traeger L, Bedrikovetski S, Nguyen TM, Lewis M, Moore JW, Sammour T. Pyridostigmine to reduce the duration of postoperative ileus after colorectal surgery – a double blinded randomised controlled trial. General Surgeons of Australia (GSA), 2023, Annual Scientific Meeting, Gold Coast, Australia.

Traeger L, Bedrikovetski S, Nguyen TM, Lewis M, Moore JW, Sammour T. Pyridostigmine to accelerate gastrointestinal recovery after colorectal surgery – a double blinded randomised controlled trial. RACS, 2023, SA Paper Day, Adelaide, Australia.

Traeger L, Bedrikovetski S, Nguyen TM, Lewis M, Moore JW, Sammour T. Pyridostigmine to accelerate gastrointestinal recovery after colorectal surgery – a double blinded randomised controlled trial. Colorectal Surgical Society Australia & New Zealand, 2023, Colorectal Spring Meeting, Gold Coast, Australia.

Traeger L, Hall T, Bedrikovetski S, Kroon HM, Dudi-Venkata N, Moore JW, Sammour T. The impact of anaesthetic reversal with acetylcholinesterase inhibitors on postoperative ileus following colorectal surgery. RACS, 2022, SA Paper Day, Adelaide, Australia.

Traeger L, Koullouros M, Bedrikovetski S, Kroon HM, Thomas ML, Moore JW, Sammour T. Cost of postoperative ileus following colorectal surgery from an Australian Institution. RACS, 2022, SA Paper Day, Adelaide, Australia.

Traeger L, Koullouros M, Bedrikovetski S, Kroon HM, Thomas ML, Moore JW, Sammour T. Cost of postoperative ileus following colorectal surgery from an Australian Institution. Tripartite Colorectal Meeting, 2022, Auckland, New Zealand.

Traeger L. Can we reduce postoperative ileus with Pyridostigmine? Royal Adelaide Hospital & Queen Elizabeth Hospital, 2022, Departmental Research Meeting, Adelaide, Australia.

Traeger L, Hall T, Bedrikovetski S, Kroon HM, Dudi-Venkata N, Moore JW, Sammour T. Impact of neuromuscular reversal agents on postoperative ileus following colorectal surgery: A multivariate analysis. RACS, 2022, ASC, Brisbane, Australia.

Traeger L, Hall T, Bedrikovetski S, Kroon HM, Dudi-Venkata N, Moore JW, Sammour T. The impact of anaesthetic reversal with acetylcholinesterase inhibitors on postoperative ileus following colorectal surgery: A retrospective cohort study. GSA, 2021, Virtual Paper Day, Adelaide, Australia.

POSTER PRESENTATIONS

Traeger L, Bedrikovetski S, Moore JW, Sammour T. Predictors of postoperative ileus following colorectal surgery: A machine learning model. RACS, 2023, ASC, Adelaide, Australia.

Traeger L, Bedrikovetski S, David R, Moore JW, Sammour T. The financial impact of sarcopenia on colorectal surgery: a single-centred cost analysis in the Australian public hospital setting. RACS, 2023, ASC, Adelaide, Australia.

Traeger L, Hall T, Bedrikovetski S, Kroon HM, Dudi-Venkata N, Moore JW, Sammour T. The impact of anaesthetic reversal with acetylcholinesterase inhibitors on postoperative ileus following colorectal surgery: A retrospective cohort study. Tripartite Colorectal Meeting, 2022, Auckland, New Zealand.

Traeger L, Dudi-Venkata N, Bedrikovetski S, Kroon HM, Moore JW, Sammour T. Use of acetylcholinesterase inhibitors in reducing postoperative ileus following abdominal surgery: A systematic review. RACS, 2022, ASC, Brisbane, Australia.

Traeger L, Koullouros M, Bedrikovetski S, Kroon HM, Thomas ML, Moore JW, Sammour T. Cost of postoperative ileus following colorectal surgery from an Australian institution. RACS, 2022, ASC, Brisbane, Australia.

RESEARCH FUNDING AND SCHOLARSHIPS RECEIVED

2021-2022 Research and Training Stipend
Scholarship, University of Adelaide, Adelaide, South Australia, Australia

2021 Royal Adelaide Hospital Colorectal Research Group Scholarship
Supplementary Scholarship, Adelaide, South Australia, Australia

2021-2022 Royal Adelaide Hospital Research Committee Dawes Top-up
Supplementary Scholarship, Adelaide, South Australia, Australia

2022-2023 Central Adelaide Local Health Network CEO Clinical Rapid Implementation Project Scheme Grant
Royal Adelaide Hospital, South Australia, Australia

2023 Royal Australasian College of Surgeon RP Jepson Scholarship
Scholarship, Adelaide, South Australia, Australia

AWARDS RECEIVED

2023 Adelaide Medical School, Department of Surgical Specialties Prize.
Florey Postgraduate Conference, Adelaide Convention Centre
University of Adelaide, Adelaide, South Australia, Australia

2023 General Surgeons Australia, John Ham Medal for Best Paper.
Annual Scientific Meeting, JW Marriott
Gold Coast, Queensland, Australia

2023 Royal Australasian College of Surgeons, Justin Miller Medal for Best Clinical Paper.
SA Paper Day
Adelaide, South Australia, Australia

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ABBREVIATIONS

Symbols

%	Percentage
$	Dollars
€	Euros
α	Alpha
ß	Beta
I_2	Inconsistency (Index of Heterogeneity)
χ^2	Chi-Squared

A

α7nAChR	α7 Nicotinic Acetylcholine Receptors
ACh	Acetylcholine
ACI	Acetylcholinesterase inhibitor
ACPO	Acute Colonic Pseudo-Obstruction
ADL	Activities of Daily Living
AI	Artificial Intelligence
AJCC	American Joint Committee on Cancer
AKI	Acute Kidney Injury
AP	Anterior Posterior
APR	Abdominoperineal Resection
ARRC	Advanced Recovery Room Care
ASA	American Society of Anaesthesiologist Physical Status Classification.
AUROC	Area Under the Receiver Operating Characteristic
ATSI	Aboriginal-Torres Strait Islanders
AUS	Australia
AUD or AU$	Australian Dollars

B

BD	Twice Daily
BMI	Body Mass Index

C

CAIP	Cholinergic Anti-Inflammatory Pathway

CALHN	Central Adelaide Local Health Network
CCF	Congestive Cardiac Failure
CCI	Comprehensive Complications Index
CCU	Cardiac Care Unit
CD	Clavien-Dindo
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclo-oxygenase
CT	Computed tomography

D

d	Days
DM	Diabetes Mellitus
DVT	Deep Vein Thrombosis

E

eGFR	Estimated Glomerular Filtration Rate
ENS	Enteric Nervous System
ERP	Enhanced Recovery Protocol
ExPANs	Extrinsic primary afferent neurons

F

G

g	Grams
GI	Gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development and Evaluations.

H

h	Hour
HOS	High Output Stoma
HR	Hazard Ratio
HREC	Human Research Ethics Committee

	HTN	Hypertension
I		
	IBD	Inflammatory Bowel Disease
	ICC	Interstitial Cells of Cajal
	ICD	International Classification of Disease
	ICU	Intensive Care Unit
	IL	Interleukin
	IM	Intramuscular
	IMTA MCQ	Institute For Medical Technology Assessment Medical Consumption Questionnaire
	IPANs	Intrinsic Primary Afferent Nerves
	IQR	Interquartile Range
	IV	Intravenous
J		
K		
	Kg	Kilogram
L		
	L	Litre
	L3	3rd Lumbar Vertebrae
	LAP	Laparoscopic
	LARS	Low Anterior Resection Syndrome
M		
	m	Metre
	Mcg	Microgram
	MEQ	Morphine Equivalents
	MeSH	Medical Subject Headings
	MFI	Modified Frailty Index
	Mg	Milligram
	min	Minute
	ml	Millilitre
	ML	Machine Learning

MLP	Multilayer Perceptron
mm	Millimetre
mmol/L	Millimole per litre

N

n	Number
NA	Not Available
NG	Nasogastric
NGT	Nasogastric Tube
NHMRC	National Health and Medical Research Council
NM	Neuromuscular
NMBD	Neuromuscular Blocking Drug
NMJ	Neuromuscular Junction
NO	Nitric Oxide
NS	Not Statistically Significant
NSAIDs	Non-steroidal anti-inflammatory drugs
NSG	Non-Sarcopenic Group
NTS	Nucleus Tractus Solitarius
NY	New York
NZ	New Zealand
NZD	New Zealand Dollar

O

OC	Open Cholecystectomy
OD	Once Daily
OR	Odds Ratio
OT	Operating theatre

P

PACS	Picture Archiving and Communication System
PCA	Patient Controlled Analgesia
PE	Pulmonary Embolism
PG	Prostaglandin
PO	Per Oral

POD	Postoperative Day
POI	Postoperative Ileus
PPOI	Prolonged Postoperative Ileus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PSM	Propensity Score-Matched
PyRICo-P	Pyridostigmine to Reduce the Incidence of Postoperative Ileus following Colorectal Surgery- Phase II Study

Q

Q8H	8 Hourly

R

RAH	Royal Adelaide Hospital
RBF	Radial Basis Function
RCT	Randomised Controlled Trial
ROC	Receiver Operator Characteristics
RR	Relative Risk

S

SAH	St Andrew's Hospital
SB	Small Bowel
SBO	Small Bowel Obstruction
SC	Subcutaneous
SD	Standard Deviation
SG	Sarcopenic Group
SMI	Skeletal Muscle Index
SOFA	Sequential Organ Failure Assessment
SP	Substance P
STIMULAX	Stimulant and Osmotic Laxatives
STROBE	Strengthening The Reporting of Observational Studies in Epidemiology

T

T test	Students T Test
TAP	Transversus Abdominis Plane

TEMS	Transanal Endoscopic Microsurgery
TNF	Tumour Necrosis Factor
TPA	Total Psoas Area
TPAI	Total Psoas Area Index
TPN	Total Parental Nutrition
TRIPOD	Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis

U

USA	United States of America
USD or US$	United States Dollar

V

vs	Versus
VIP	Vasoactive Intestinal Peptide
VNS	Vagal Nerve Stimulation
VTE	Venous Thromboembolism

W

X

Y

Z

CHAPTER 1: INTRODUCTION

1.1 COMPLICATIONS

Colorectal surgery is a prominent aspect of general surgical practice, encompassing various conditions that affect the abdomen, such as colon and rectal malignancy. Performing operative treatments for these conditions carries the risk of complications for patients. The resulting morbidity adversely affects patients by reducing their autonomy, prolonging their hospital stay, and even leading to mortality.[1] Moreover, this has a substantial economic impact due to the extensive utilisation of healthcare resources.[2] In the context of colorectal surgery, one complication that deserves particular attention is postoperative ileus (POI), the most prevalent complication associated with this type of surgery.[3, 4]

The root of colorectal surgery can be traced back to ancient Egypt, where physicians treating intestinal parasitosis recognised the significance of gastrointestinal (GI) function.[5] Historical medical texts, such as the Talmud, stress the importance of regular bowel activity as vital for life.[5] Following advancements in colonic resection, with the first being performed in 1823, there have been gradual improvements in sterility, operative time, anatomical knowledge and surgical techniques.[5] This has gradually decreased mortality rates in colorectal surgery.

Despite these improvements, morbidity following surgery continues to impose a significant burden on patients and healthcare systems alike. In Australia, for instance, abdominal surgeries accounted for 21% of all elective surgeries conducted in public hospitals, contributing to a healthcare cost of $66.4 billion in 2019-2020.[6] Of these procedures, over 15,000 are considered bowel-specific or colorectal surgery. The Australian healthcare system spent an extra AU$460 million (16% of healthcare expenditure) on complications in 2003-2004.[7] In the United States, projected surgical healthcare costs are set to exceed US$1 Trillion by 2025.[2]

Patients undergoing abdominal surgery face considerable risks. Risks vary from bleeding, wound complications, anastomotic leakage and medical complications.[8] However, one of the most common complications is POI, representing the delay in the return of normal GI function. POI represents a significant complication and affects patient autonomy and experience following surgery.[9] Unfortunately, current strategies to prevent POI have had varied success.

Further research and development of improved approaches to address POI and improve outcomes for colorectal surgical patients are required.

1.2 WHAT IS POSTOPERATIVE ILEUS?

POI is a term encompassing a constellation of symptoms that result from abnormal GI motility that often follows surgery and has been the subject of investigation for over a century.[10] These symptoms include but are not limited to nausea, vomiting, abdominal distention and pain, and constipation, often necessitating interventions such as nasogastric (NG) tubes placed through the nose to drain the stomach and alleviate discomfort.[11, 12]

POI is common following intra-abdominal and extra-abdominal procedures, such as spinal cases.[4, 13-16] The incidence of POI following abdominal surgery can vary significantly, depending on the definition used, the surgical specialty and the specific operation performed, ranging from 3-30%.[4, 14-17] This variability is primarily attributed to the diversity of surgical disciplines. Intra-abdominal surgery, which encompasses procedures on the GI tract (oesophagus, stomach, small and large bowel) and urogenital tract (kidney, ureters, bladder, prostate, uterus, ovaries) carries a high risk for POI; for example, hysterectomy carries a risk of around 9% compared to colorectal with an incidence of 10-30%.[4, 13-16] Extra-abdominal procedures carry a lower risk, with spinal surgery having a risk of <10%.[18]

Colorectal surgery, particularly large bowel resections and anastomoses, carries the highest risk of POI, which is explored further in our discussion on risk factors (page 14).

The mechanisms underlying the development of POI are multifactorial and explored on page 8. Ongoing controversy surrounds the determination of when normal GI function return becomes pathological.[4, 15] Notably, the literature employs a range of definitions for POI.[4, 15] These include POI, characterised as the period of altered GI motility during the postoperative recovery phase, that limits the normal absorption of nutrients and elimination of waste.[4, 19] However, challenges arise in distinguishing types of POI, resulting in further classification using terms like obligatory, prolonged, primary, and secondary.[4, 19, 20]

The term ‘POI’ is often used interchangeably with ‘obligatory POI’, which refers to the initial phase of GI recovery influenced by perioperative factors such as the specific procedure performed.[19, 20] Adding to the complexity, POI is often interchangeably used in the literature as ‘Prolonged POI’, signifying the period when the recovery of normal GI motility does not occur within a defined timeframe or when POI extends beyond the obligatory phase. This creates ongoing debate about where to draw the line between normal GI recovery and POI or prolonged POI and whether these represent a continuous spectrum or differing conditions. Existing literature presents varying perspectives, with different studies proposing recovery periods ranging between 1 to 7 days, with the majority utilising postoperative day 4 or 5 as a common benchmark to distinguish the obligatory recovery phase from pathological POI.[4, 21]

Furthermore, POI can be further categorised as primary or secondary POI. ‘Primary POI’ is when POI results following the operation itself, while ‘Secondary POI’ results from another complication, such as an anastomotic leak resulting in a sepsis-induced POI, representing

a different pathological process.[22, 23] This can sometimes be called recurrent or paralytic ileus.[19] Overall, the process is imperfect.

Various methods are also used to measure the return of GI function and quantify POI's effects.[15, 24] The most effective measure for evaluating recovery of bowel function appears to be the time to achieving GI-2.[19, 25] It is a composite measure of time to first stool and time to oral and solid diet tolerance. This measure is straightforward, assesses obligatory POI, and directly correlates with the normal return of GI function as measured by colonic transit scintigraphy.[19, 25] However, it does have a limitation, as it may not adequately capture reversals in a patients recovery trajectory. In addition to GI-2, another measure of GI recovery is GI-3, which differs to GI-2 as it considers the time to first stool or flatus and oral diet tolerance.[15, 19, 25] These metrics evaluate both upper GI recovery (diet tolerance) and the recovery of the lower GI tract (time to stool/flatus). Nevertheless, GI-3 relies on patients to report flatus, which may not be noticed by patients, potentially limiting its accuracy.[15, 19, 25]

Other measures include inserting an NG tube, a clearly defined endpoint that suffers from clinician variability and patient choices.[19] Traditional markers, like time to passage of first stool and time to first flatus, are also used to gauge colonic recovery. However, the time to flatus may not be reported or noticed by patients, and the time to first stool does not measure diet tolerance.[15, 26] Additionally, vomiting as a measure is influenced by multiple factors, such as anaesthetic and postoperative opioid use and is affected by antiemetic usage.[15]

In addition to the diversity of potential methods of defining and measuring GI recovery or POI, many papers retrospectively identify afflicted patients using coding data, such as patients being billed for this complication and having an ICD-9 code placed against their

admission.[27-31] However, this often underestimates the incidence of POI considerably as it can only include patients with an intervention for POI.[32]

The issues and complexities surrounding the definition and measurement of POI are highlighted above. To enhance the evaluation of clinical studies, the Tripartite Gastrointestinal Recovery Post-operative Ileus Group, has developed a core outcome set for POI relevant to patients undergoing intestinal surgery.[33] In a collaborative effort, 155 stakeholders reached a consensus on nine domains, encompassing 23 outcomes deemed central to POI assessment.

The domains and outcomes included:

- Incidence and duration of POI (which combined POI and PPOI as a single construct).
    - Including core outcomes of incidence of POI and duration of POI.
- Vomiting and gastric decompression.
    - Including core outcomes of incidence of nausea and vomiting, duration of vomiting, need for NG placement and volumes of NG aspirates.
- The severity of abdominal pain.
- Nutritional factors.
    - Including core outcomes of nutritional status, time without adequate nutritional intake and need for parenteral nutrition.
- Return of gut function.
    - Including core outcomes of measuring GI recovery using a validated tool, time to first stoma output, and readiness for discharge.
- Patient experience or patient-reported perception of POI.
- Complications arising from POI.

    - Including morbidity, septic complications, admission to an intensive care unit, or organ injury/failure.
- Readmission rates.
- Predisposing factors for POI.
    - Including abdominal infection rates, anastomotic leak, peritonitis and enterotomy.

The above outcome set is the first step towards improving the reporting of POI and improving research related to POI, the above features representing the most critical factors involved with POI. However, it was acknowledged that a standardised definition for POI still needed to be provided.

For this thesis, I have chosen to simplify the above definitions. I have defined the period following surgery for GI function to return using the validated outcome measure of GI-2. I have used the term POI to refer to when this delay in return of GI function becomes pathological and defined this as not achieving GI-2 by the end of day four postoperatively.

1.3 MECHANISMS OF POSTOPERATIVE ILEUS

The mechanism by which POI occurs is multifactorial, consisting of inflammatory cell activation, autonomic dysfunction, opioid receptor agonism, modulation of GI hormones, and electrolyte derangement. This can be further categorised into three phases. The initial neurogenic response is followed by an inflammatory response, further exacerbated by postoperative factors.[19, 34, 35] Recent research has shed light on the diverse mechanisms of POI and potential therapeutic approaches.[10, 19, 34]

1.3.1 NEURAL RESPONSE.

The neural response occurs immediately during surgery and can have a prolonged inhibitory effect. Normal gut motility relies on the intricate coordination of enteric neural circuits, which coordinate patterns of circular and longitudinal smooth muscle layers along the GI tract.[10, 36, 37] This coordinated excitation and inhibition of the bowel is partly controlled by enteric nerve cells situated in the myenteric and submucosal plexuses.[36, 37]

The GI tract's smooth muscle receives innervation from excitatory and inhibitory motor neurons. These neurons are driven by complex sensory and interneural pathways, giving rise to various motor patterns.[37] These differing intestinal motor patterns are modulated by the extrinsic efferent autonomic nervous system, which includes sympathetic and parasympathetic divisions. These modulations are related to the patient's changing needs, for example, exercise and post-meals.[38]

When triggered, the extrinsic sensory neurons in the gut wall cause the central nervous system (CNS) to register symptoms such as feeling full, nausea, pain, and urgency.[38] Mechano-receptors respond to mechanical distension of the gut wall, and chemo-receptors react to changes in pH or the presence of toxins or nutrients, providing sensory input to the CNS.[36] They also influence the autonomic pathways, thereby altering gut

function. These nerve pathways deliver afferent communication via the spinal and vagal pathways.

Spinal extrinsic primary afferent neurons (ExPANs) are found in the thoracolumbar and lumbosacral dorsal root ganglia and project to the CNS at the spinal level. The sympathetic supply to the enteric nervous system (ENS), provided by the spinal neurons, exerts an inhibitory effect on gut motility.[36, 37] The sympathetic supply is in the prevertebral ganglia (celiac, mesenteric, and pelvic ganglia).[39] Noradrenaline, the transmitter released by these neurons, affects enteric neurons and inhibits gut motility via pre-synaptic α-2 adrenergic receptors.[40] Postganglionic sympathetic neurons supply the myenteric ganglia, submucosal ganglia and intestinal blood vessels.[10] This sympathetic nervous system reduces blood flow to the gut, decreases peristalsis, and inhibits digestive secretions in response to stress, part of the 'fight or flight response'.[41]

The vagal pathways provide the parasympathetic supply to the bowel. Vagal ExPANs carry sensory information to the vagus nerve's nodose and superior (jugular) ganglia. Vagal nerves project to the nucleus of the solitary tract in the brainstem, which, in turn, stimulates the dorsal raphe nucleus.[36] Parasympathetic input is supplied from the dorsal motor nucleus of the vagus, located within the brainstem, which terminates within the submucosal and mucosal plexus, stimulating excitatory motor neurons.[36, 42] This primarily promotes digestion and relaxation of the GI tract.

Additionally, intrinsic primary afferent nerves (IPANs) are located within the submucosa and myenteric plexus. These plexuses project signals to one another, with submucosal IPANs primarily functioning as secretomotor neurons, while myenteric IPANs project to inhibitory and excitatory motor neurons.[36] Furthermore, additional pacemaker cells

generate myogenic rhythmic depolarisations within the smooth muscle. These cells include interstitial cells of Cajal (ICC), which are discussed further below.[43]

Delving further into the above mechanisms, sensory information is provided during surgery via two pathways or wounds.

Somatic wounds are created by incising the abdominal wall. Anterior and lateral branches of the ventral rami of the lower intercostal and lumbar nerves provide sensory innervation from the abdominal wall.[44, 45] Nociceptive stimuli are carried to the posterior column of the spinal cord, causing localisation of pain and triggering a local unbalanced autonomic response.[19, 34]

Visceral wounds are created through the peritoneal incision and bowel handling. When injured, the peritoneum covers the intestinal viscera and activates the inflammatory cascade by triggering the mechanoreceptors and chemoreceptors.[45, 46] This sensory information provided via the vagus nerve to the brainstem is vital in developing POI. Additionally, these chemo-receptors have Interleukin(IL)-1 receptors activated by humoral changes secondary to the inflammatory response described below.[45, 47]

1.3.2 EFFERENT PATHWAYS

Post-surgery, there is an autonomic shift towards sympathetic outflow.[10, 48] Normal vagal nerve parasympathetic output is delivered via the dorsal motor via the vagal and splanchnic nerves[36, 42], causing postganglionic neurons to release acetylcholine (Ach), increasing smooth muscle excitability and contractility via the M2 and M3 muscarinic receptors [49, 50] However, in POI, there is an exaggerated sympathetic response.[69] The sympathetic effects originate from the lateral horn of the spinal cord as a response to nociceptors responding to

mechano- and chemoreceptors. The adrenergic response and release of catecholamines leads to activation of α2-adrenoceptors, acting in the parasympathetic cholinergic nerves, inhibiting the release of ACh, which stimulates nitric oxide (NO) via myocytes.[51, 52] This reduces myocyte tonicity and contractility.[53-55]

1.3.3 INFLAMMATORY RESPONSE

During an operation, the peritoneum is breached, and the bowel is handled. This results in a release of proinflammatory mediators.[56, 57] These inflammatory mediators include, but are not limited to, histamine, prostanoids, and IL-6 and 8. As part of this inflammatory cascade, mast cells in the peritoneum and muscularis propria of the bowel are activated, as well as monocytes and macrophages.[58, 59] This is likely due to damage-associated molecular patterns and pathogen-associated molecular patterns.[45]

Macrophages within the muscularis near the myenteric plexus play a vital role in developing POI.[60-62] Activated macrophages increase chemokines (monocyte chemoattractant protein-1 and macrophage inflammatory protein-1α, proinflammatory cytokines (IL-1 and 6, TNF-α) and integrins.[24, 45, 63] The release of these agents results in the up-regulation of cell adhesion molecules, causing the passage of proinflammatory cells into the intestinal muscularis.[64] The invasion of these cells, increases NO and prostaglandin (PG) production, thus resulting in decreased contractility of smooth muscle activity.[45] Cyclo-oxygenase-2 dependent PG E2 and NO are also released as part of the inflammatory pathway, known for their effect as smooth muscle relaxants.[45, 58, 65, 66] The resultant hyperpermeability due to inflammation impairs myotonic contractions.[45, 67] This is contributed to by increased perioperative fluid administration.[68] Also, due to inflammation, the bowel may become ischaemic due to the inflammatory state and operative techniques reducing blood flow.[69, 70]

1.3.4 GI HORMONES AND NEUROPEPTIDES

Normal gut motility results from the impact of GI hormones and neuropeptides, such as somatostatin, secretin, substance P (SP), vasoactive intestinal peptide (VIP) and ghrelin.[71-73] Surgical insults and decreased oral intake reduce normal GI hormone levels.[74-77] These hormones mediate the neuro-immuno-humoral inflammatory response to tissue injury. Both SP and VIP have agonist and antagonist properties in gut recovery, making their role in the mechanism of POI unclear.[74-77] Ghrelin, on the other hand is released during the fasting state from parietal cells of the gastric fundus, and increase appetite, and have been the subject of further investigations and trials.[73, 78]

1.3.5 DISRUPTION OF INTESTINAL CONTINUITY

Specific to abdominal operations is bowel anastomosis. Highlighted above is the importance of the ENS. When the bowel is resected, the electromechanical coupling is physically disrupted. Interstitial cells of Cajal (ICC) networks are essential in propagating peristalsis and, when affected, contribute to POI.[79, 80] When the ICC is disrupted, this alters the contraction. Colonic tissue peristalsis relies on the ENS and the ICC network, while the small bowel depends more on the myenteric plexus.[50, 81, 82] This disruption of the ICC has a more substantial effect on colorectal cases than small bowel procedures. However, it represents an unmodifiable risk factor.[4, 34]

1.3.6 POSTOPERATIVE FACTORS

1.3.6.1 ELECTROLYTE DERANGEMENT AND FLUID USE

Disturbances in electrolytes have well-documented effects on gut motility.[78] It is unclear whether the electrolyte disturbances result in myenteric dysfunction or whether they result from fluid shifts related to POI.[83] Electrolyte disturbances such as hypokalaemia, hypocalcaemia, and hyponatraemia are commonly associated with POI and should

rigorously be corrected as part of an ERP.[83, 84] Fluid management also has been implicated in the development of POI. However, its overall effect remains contentious.[1, 85-88] Excessive intravenous fluids during the perioperative period can increase bowel wall oedema and precipitate electrolyte disturbance, impairing GI motility.

1.3.6.2 OPIOID USE

Opioids have a drastic effect on GI motility. Opioids are given in the perioperative and postoperative periods, directly acting on the CNS and peripheral μ-opioid receptors.[83] They are important for patients' comfort; however, activating the peripheral μ-opioid receptors inhibits ACh, increasing smooth muscle tone and impairing GI motility.[14, 83, 89]

1.3.7 RECTO-SIGMOID BRAKE

In addition to the above-discussed mechanisms, there is growing debate about the physiological recovery of the GI tract. Previously, GI motility was thought to recover in phases, starting with small bowel (<24 Hours), stomach (24-48 hours) and colon (>48 hours) last.[34] High-resolution colonic manometry has recently altered this thinking, with cyclic motor patterns starting in the distal colon soon after anaesthesia induction.[90, 91] These motor complexes in the distal colon are called the ‘rectosigmoid brake’. They often are triggered by calorie-rich meals, morning waking and electrical stimulation, limiting the amount of rectal filling and maintaining continence.[92-96] Additionally there is an ‘ileal brake’, that delays gastric emptying and small bowel transit in response to lipids, protein and carbohydrates in the distal ileum.[73] The interplay between the effect of nutrients and distension in the small bowel and colon, may contribute to differences in the return of GI function between left and right colonic resections.[73, 97-99]

1.4 RISK FACTORS FOR POSTOPERATIVE ILEUS

Among all abdominal surgeries, colorectal surgery has the highest incidence of POI. This elevated risk can be attributed to a complex interplay of patient-related, operative and postoperative risk factors.[17, 63, 84, 100, 101] Colorectal aspects such as the handling of the bowel, mobilisation of the splenic flexure, formation of a stoma, the use of an open surgical approach and rectal resections, have been identified as particularly predisposing factors for the development of POI.[63, 101, 102]

A recent meta-analysis has identified several risk factors associated with POI.[101] Notably, the GRADE evidence suggests a moderate association with an open approach/laparotomy (OR 2.47, 95%CI 1.77–3.44, I_2=69%). However, the quality of GRADE evidence was low to very low quality for other factors such as male sex (OR 1.43, 95%CI 1.25-1.63, I_2=58%), older age, (64.84 ± 16.85 vs. 61.47 ± 18.03, MD 3.17, 95%CI 1.63-4.71, I_2 = 47%), cardiac comorbidities (OR 1.54, 95%CI 1.19-2.00, I_2 = 0%), previous abdominal surgery (OR1.44, 95%CI 1.19-2.00, I_2 = 0%), and stoma formation (OR 1.44, 95%CI 1.04-1.98, I_2 = 70%).[101] The well-known risk factor of opioid consumption was not included in the meta-analysis due to heterogeneity in measurements.[83, 89, 103]

Notably, potential risk factors like body mass index (BMI), diabetes mellitus (DM), smoking, alcohol consumption, colorectal malignancy, type of colectomy, anastomosis type and prolonged operative duration lacked sufficient evidence to be conclusively linked to POI.[101] Other potential risk factors may include emergency operations, higher ASA classification, chronic obstructive pulmonary disease, increased perioperative transfusion/anaemia, preoperative hypoalbuminemia, and postoperative hypokalaemia.[14, 63, 83, 101, 104]

Additionally, it should be noted that the meta-analysis indicated limitations in the existing literature. Many studies are retrospective and lack an exhaustive consideration of potential risk factors. Variability in the definitions of POI, reliance on subjective clinical assessments, and the use of univariate/multivariate analyses hinder a comprehensive understanding of POI risk factors. Moreover, current statistical methods do not allow for the ranking of variable importance.

There is a potential gap in the literature on using artificial intelligence (AI) to predict POI and identify new risk factors associated with POI.

Artificial intelligence(AI) has the potential to improve the accuracy of POI prediction by analysing large volumes of data and identifying complex non-linear patterns that traditional statistical methods may not identify.[105] Machine learning (ML), a subset of AI, has been able to predict mortality in orthopaedic trauma and cardiac surgery and complications following laparotomy.[106-108] In colorectal-specific papers, ML has been used to predict metastasis, response to chemotherapy, postoperative complications and survival.[109, 110] However, limited studies[111, 112], have investigated the association between risk factors and POI, highlighting a promising avenue for future research.

1.5 IMPACT OF POSTOPERATIVE ILEUS ON PATIENT RECOVERY

POI exerts a profound and detrimental impact on patient outcomes, affecting both short-term recovery and long-term survival whilst diminishing the overall quality of life.[12, 113] The repercussions of POI lead to increased end-organ dysfunction, 30-day mortality and prolonged hospital stay.[12]

POI manifests through distressing symptoms of nausea, vomiting, diet intolerance, abdominal pain and distension, and constipation in the short term. These symptoms are not only uncomfortable, unpleasant and disheartening but can lead to respiratory complications. The resultant abdominal distension causes impaired breathing, reduced tidal volumes, and vomiting, which increases the risk of atelectasis and aspiration pneumonitis/pneumonia.[114-116] To manage POI, healthcare providers often insert a nasogastric (NG) tube to decompress the stomach and minimise the risk of vomiting. This has been shown to occur in approximately 22.5% of patients undergoing left or right colonic resection.[117] Unfortunately, this procedure is distressing for patients, often paradoxically leading to vomiting.[118] The established link between vomiting, aspiration and atelectasis, can lead to pneumonia, requiring critical care admission due to respiratory failure.[119]

Beyond respiratory complications, the lack of proper nutrition predisposes patients to delayed wound healing, primarily stemming from nutritional deficiencies and electrolyte disturbances.[116, 120, 121] This further increases the likelihood of complications such as an anastomotic leak, one of the most morbid complications following abdominal surgery.[28, 122, 123]

Moreover, POI significantly impacts the length of patient stay – often doubling patients' hospitalisation requirements.[12, 14] This extended stay takes a significant toll on the patient's psychological well-being and autonomy.[9] Along with the increased length of stay, the presence of an NG tube negatively impacts their quality of life and increases stress, further affecting their recovery.[124, 125]

Studies have indicated that preventing POI could lead to a 33% reduction in delayed discharges, 20.7% fewer readmissions, and 20% lower mortality rates, underlining the critical importance of mitigating POI to improve recovery.[12]

1.6 ECONOMIC IMPACT OF POSTOPERATIVE ILEUS

The secondary effects of POI on patients also result in a significant financial burden for healthcare services.[125] POI can increase hospital costs by a staggering 50-100% globally, significantly contributing to the financial strain on healthcare systems.[27, 28, 126]

Previous research has demonstrated various factors driving these costs, including increased staffing costs, imaging, pharmacy and laboratory services.[27-31, 125-127] In addition to prolonged hospitalisation, imaging use is escalated to investigate factors such as anastomotic leakage resulting in septic ileus or diagnosing POI-related complications, such as pneumonia. Additionally, due to heightened service requirements and greater opioid prescribing, pharmacy costs increase.[27]

Furthermore, patients with POI are predisposed to other complications such as pneumonia, deep vein thrombosis and cardiac events, which add to healthcare costs.[12, 128] Regardless of the severity and nature of complications, the cost of hospital admission approximately doubles.[129] To put this into perspective, POI as a single complication is estimated to cost over US$1 billion annually in the US alone.[27-29, 126, 127] Some studies have shown an increase of over US$8,000 per patient in hospital care due to POI.[12, 127]

There was a notable absence of reports regarding the costs of POI in Australia. Consequently, this PhD investigated the financial implications of POI following colorectal

surgery in an Australian public hospital and provided additional insights into the global cost of POI.

1.7 POTENTIAL THERAPEUTIC OPTIONS FOR POSTOPERATIVE ILEUS

Given the negative impact POI has on recovery, and the significant financial impact, there has been a variety of different strategies to prevent and or treat POI.

1.7.1 REDUCING SURGICAL STIMULATION

Strategies to reduce the effect of stimulation of the gut have resulted in the importance of performing minimally invasive surgery – particularly laparoscopic surgery. Laparoscopic surgery does have moderate benefits in reducing POI; however, POI persists.[130, 131] When possible, a minimally invasive approach will lessen the visceral and somatic wounds while also helping to reduce opioid requirements, thus improving the return of GI function.[132, 133] In addition the use of local anaesthetic and epidural anaesthesia may reduce the impact these wounds have on the development of POI.[134-137]

1.7.2 TARGETING THE NEURAL PATHWAY

Sympathetic blockade has been suggested as a method of improving POI.[138, 139] Animal studies have trialled blocking noradrenaline release and using α2-adrenoceptor agonists to improve small bowel transit.[138, 140] Additionally, further studies have trialled β-adrenoreceptor blocker (propranolol), improving the time to first stool. However, its actual effect remains contentious.[141-143] Moreover, other researchers have trialled sympathetic blockade and cholinergic activation, improving gut function; however, these approaches were abandoned due to side effects.[142]

As described above, the vagus nerve regulates gut motility and the response to inflammation, ensuring homeostasis. Enteric neurons of the myenteric plexus are close to

macrophages in the muscularis.[45, 144] Vagal efferents secrete ACh, which activates the α7-subtype of the nicotinic ACh receptor (α7nAChR) on macrophages. α7nAChR is a significant part of the cholinergic anti-inflammatory pathway, and through the PI3K/Akt, NF-kappaB, JAK2/STAT3, decreases the production of the proinflammatory cytokines such as TNF-α, IL-1, IL-6 through various pathways.[45, 144] It also upregulates the activity of IL-10, which is an anti-inflammatory factor.[145]

Pharmacological alternatives could mimic the vagus nerve's action, stimulating the release of Ach from enteric neurons along the digestive tract. To this purpose, selective 5-Ht4 agonists (prucalopride) have been trialled to improve GI recovery. Prucalopride works by increasing ACh release from vagal neurons.[146, 147] Two RCTs have been performed to assess the use of prucalopride to target the vagal pathway in POI. In a 110-patient RCT, patients receiving prucalopride had a significant reduction in time to flatus and defecation and a one-day decrease in length of stay.[146] Additionally, prolonged ileus (>5 days) was significantly lower in the intervention arm (16.4% vs. 34.5%, p=0.026). However, this was not confirmed in a 148-patient double blinded RCT by Milne et al., who showed no improvements in GI-2 or POI.[147] Additionally, in a study comparing Whipple's procedures in humans against rat studies, preoperative administration of prucalopride was associated with a reduction in POI. [148] Acetylcholinesterase inhibitors (ACIs) have the potential to act similarly and are discussed further on page 31.

Animal studies have largely demonstrated the importance of vagal nerve stimulation (VNS) and reduction in inflammatory markers.[148, 149] Additionally, other methods of VNS have been investigated in humans. In laparotomies, VNS reduced inflammatory mediators IL-6 and IL-8.[150] In practice, dissecting the vagus nerve to stimulate it intraoperatively is associated with the risk of injury to the subdiaphragmatic oesophagus and prolongs theatre time. Trials of

non-invasive VNS stimulation are also ongoing. The non-invasive VNS stimulator (GammaCore® device (electroCore Inc.)) was usable in a 40-patient, parallel-group, RCT of cervical VNS without safety concerns. However, it was not powered to determine differences in GI outcomes.[151] Additionally, chewing gum has been suggested to increase gastric emptying and reducing gut inflammation by activating the vagus nerve; however, studies have not proven this link effectively reduces POI.[152-154] Through these trials, I see the value of VNS.

1.7.3 TARGETING THE INFLAMMATORY RESPONSE.

Enhanced recovery protocols (ERPs) are standardised perioperative protocols that aim to improve surgical outcomes, by placing emphasis on optimising the patients physiology. Since their adoption, they have had improvements in complications and length of stay, especially in colorectal surgery.[87, 155] They broadly involve a multimodal approach to improve recovery, with preoperative, intraoperative, and postoperative strategies.[1, 85-87] Preoperatively, they target education, optimisation, nutritional support, reducing fasting times, and bowel preparation.[156] As part of the preoperative counselling, they discuss potential complications and expectant recovery, allowing patients to understand and take part in their recovery.[87, 155] Intraoperatively, ERPs attempt to reduce postoperative nausea and vomiting by using short-acting anaesthetic agents, reducing opioid usage, maintaining euvolemia, and using minimally invasive surgery. Additionally, postoperative strategies involve opioid-sparing strategies, maintaining euvolemia, early nutrition and mobilisation, avoiding NG tubes and urinary catheters and aiming for early discharge.[1] The implementation of ERPs has shown promising results and could improve recovery significantly. However, the improvements seen in recovery cannot be attributed to a single intervention provided and target many potential causes and consequences of POI.[87, 155]

As part of the ERPs, efforts have been made to modulate the inflammatory cascade associated with POI using non-steroidal anti-inflammatory drugs (NSAIDs).[157, 158] This is primarily due to their anti-inflammatory properties at both the mucosal and gut wall level, as well as reducing opioid consumption.[159] However, there remains concern about the risk of acute kidney injury and the potential for anastomotic leak, and overall, the literature remains undecided on the utility of NSAIDS to improve GI recovery.[157, 160-163] In a recent prospective multicentre cohort study of 4164 patients, NSAID use did not improve GI recovery, anastomotic leak rates or acute kidney injury; however, it had a significant reduction in opioid use.[158] In addition, ERPs have been shown to improve the autonomic imbalance that results from surgery.[164]

As part of an ERP specific interventions have been included to improve GI recovery. ERP suggests an early return to nutrition is safe and effective in the postoperative period to improve GI recovery, however a recent review demonstrated only six out of ten studies RCTs showed a reduction in time to tolerance of diet or flatus/stool.[165] Additionally, a previous systematic review assessing intervention, noted 37 differing ERPs. Twenty-four studies included laxatives, 13 chewing gum, six alvimopan, four lactulose, two neostigmine, and two bisacodyl.[166] Overall, the evidence is weak for all interventions, apart from alvimopan, in improving GI recovery, incidence of POI, and length of stay.

1.7.4 TARGETING GI HORMONES

To improve GI recovery, trials have investigated Ghrelin for its prokinetic properties.[167] In rat studies, the effects of POI were considerably decreased with the use of ghrelin.[168] In a phase 2b multicentred safety study, ghrelin did improve GI recovery in the first 72 hours post-surgery. Further studies have demonstrated the safety of ghrelin postoperatively, but other trials are required.[169]

1.7.5 REDUCING OPIOID USE

The opioid antagonist alvimopan has the most significant evidence for reducing POI. It antagonises the opioid effects but only acts peripherally, thus not reducing the analgesic effects. There have been a variety of RCTs demonstrating increased GI recovery and reduced opioid consumption; however, it is only available for use in the United States.[170-175] Other medications, such as methylnatrexone, have also been trialled.[176, 177] Also, due to other opioid reducing strategies, the ongoing efficacy of alvimopan and methylnatrexone, may mean its clinical usefulness moving forward is reduced.

Other methods of reducing opioid use include the use of multimodal analgesia. Multimodal analgesia, part of a current ERP, can reduce opioid requirements.[178] This consists of using epidurals and Transversus Abdominis Plane (TAP) catheters. TAP catheters and epidurals can potentially improve the return of gut function by reducing opioid consumption. However, their ability to prevent POI remains guarded.[134-137]

Furthermore, during anaesthesia, apart from opioids, alternative agents can also impact the recovery of GI function and potentially impact GI recovery. Relevant to this thesis, ACIs and anticholinergic medications in neuromuscular blockage reversal could also affect POI development during anaesthesia. This is discussed further on page 28, and the potential use of alternative agents, namely sugammadex.

1.7.6 FLUID MANAGEMENT

The importance of fluid management has been contentious in the literature, with some papers confirming restricting IV fluid use improves GI recovery and others demonstrating no difference.[1, 68, 85-88, 179, 180] Despite this forming part of an ERP, it is unclear if the earlier

GI recovery resulting from ERP application relates to goal-directed intravenous fluid usage, both preventing and treating the effects of POI.[181-183]

Due to bowel oedema's importance to GI recovery, Gastrografin has been trialled to treat established POI. Gastrografin is a water-soluble radiological contrast media and works via hyperosmosis, drawing fluid into the bowel lumen. In an 80-patient RCT, Gastrografin did not improve GI recovery regarding nausea, vomiting, or oral diet tolerance.[184] Overall, it did improve the time to first flatus or stool and shortened the duration of POI. However, when pooled with an additional study, no difference was noted in the duration of POI.[185, 186]

Despite the wide variety of methods used to prevent and treat POI, it persists as a major complication. However, there lies promise in targeting the neural pathways by which POI occurs.

1.8 ACETYLCHOLINESTERASE INHIBITORS

Cholinesterase is an enzyme that plays a crucial role in the termination of neuron impulses by hydrolysing ACh into acetic acid and choline.[187] It is predominantly found at the neuromuscular junction, which returns cholinergic neurons to their resting state after activation. Acetylcholinesterase is the primary form of cholinesterase and is abundant in various tissues, including nerves, muscles, central and peripheral tissues, and motor and sensory fibres.[187] It is particularly prevalent in motor neurons. On the other hand, ACh is a neurotransmitter in the autonomic ganglia, autonomic innervated organs, neuromuscular junction and the CNS. It plays a crucial role in various physiological functions.[187-190]

The hydrolysis of ACh by acetylcholinesterase occurs at a remarkable rate of approximately 25,000 molecules per second.[191] The rapid breakdown of ACh is essential

for terminating neuron impulses. However, certain drugs, known as acetylcholinesterase inhibitors (ACIs), can prevent the breakdown of ACh, increasing its levels and duration of action (Figure 1).

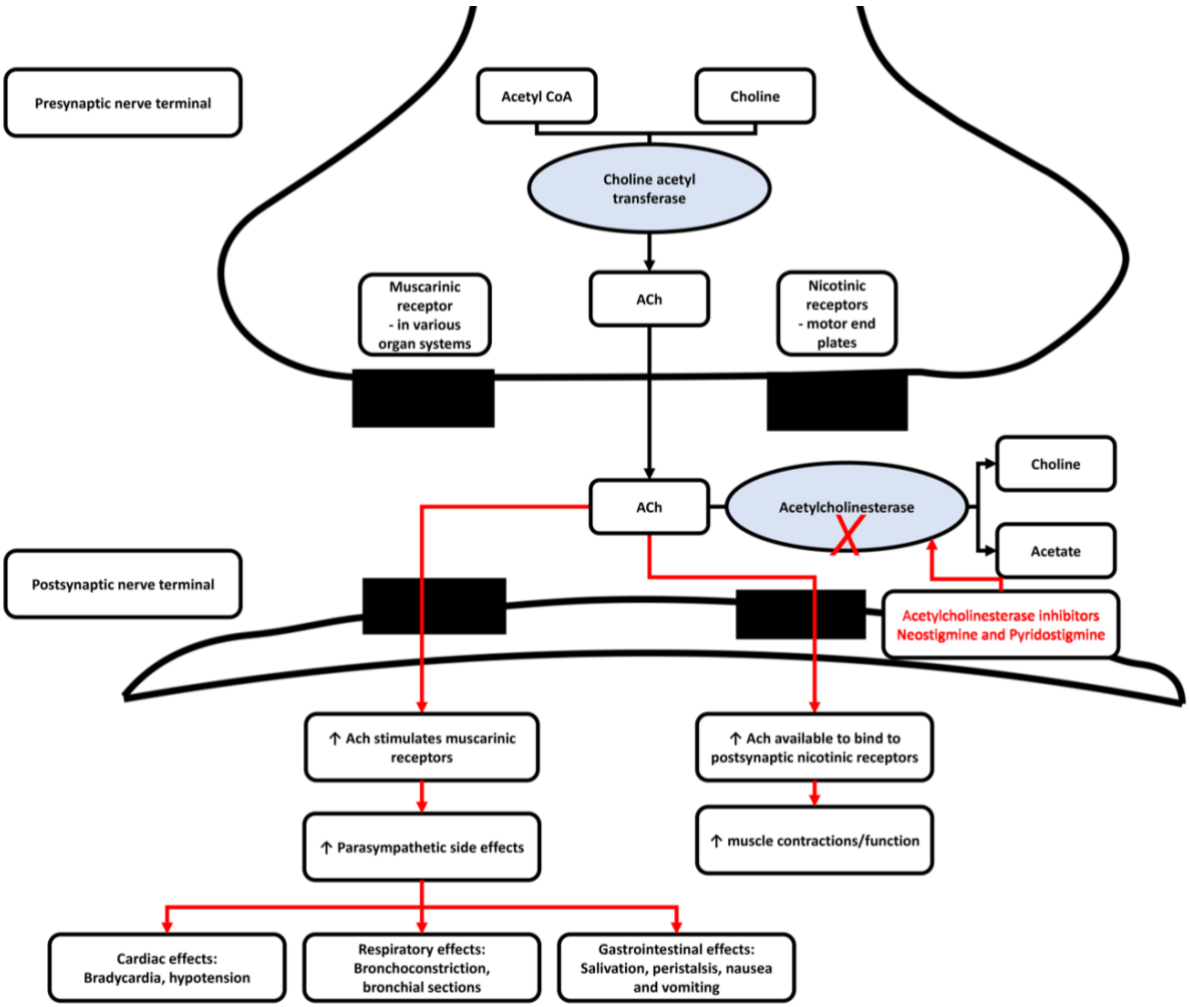

Figure 1. Action of acetylcholinesterase inhibitors

Red arrows indicated acetylcholinesterase inhibitors' effect in preventing Acetylcholine breakdown (ACh). Blue circles indicate enzymes.

Two common inhibitors are neostigmine and pyridostigmine. Neostigmine is most commonly used to reverse the effect of non-depolarising neuromuscular blocking agents following surgery, returning contractility to muscles allowing patients to maintain respiratory function following anaesthesia.[192] They also have various clinical uses in myasthenia gravis, acute colonic pseudo-obstruction (ACPO), Alzheimer's disease, atonic bladder, glaucoma, anticholinergic overdose and potentially in POI.[188, 191]

Neostigmine is an oxy-diaphoretic inhibitor and binds to the anionic site of the acetylcholinesterase, forming a covalent bond and slows the degradation of ACh.[188] Neostigmine is primarily administered intravenously, exhibiting peak effect at around 7-10 minutes, and has a duration of action of about 55-75 minutes. Due to its quaternary nitrogen structure, it is excreted renally and does not cross the blood-brain barrier.[192]

Pyridostigmine is an analogue of neostigmine but is approximately one-quarter of the potency. It forms a covalent bond with acetylcholinesterase and is not soluble in lipids.[191] Its onset of action occurs in over 16 minutes, with effects lasting approximately 6 hours. When administered orally, it has a half-life of 177 minutes.[188] Since the 1950s, pyridostigmine has been employed in the treatment of Myasthenia Gravis, an autoimmune disease characterised by the presence of autoantibodies against the nicotinic ACh receptor.[193] Pyridostigmine binds to acetylcholinesterase, thereby delaying ACh hydrolysis, prolonging ACh's availability to the defective receptor, and thus allowing short-term relief of Myasthenia Gravis symptoms.[188, 193]

ACIs can lead to increased firing within the autonomic nervous systems, which may result in muscarinic side effects. These effects manifest as cholinergic side effects, including abdominal cramps, hypersalivation, and vomiting. Other reported side effects may include

diaphoresis, pre-syncope, muscle fasciculations, fatigue, nausea, urinary urgency, increased bronchial secretions, rash, and blurred vision.[193-196] Additionally, they can cause cardiac complications such as bradycardia, heart block, and life-threatening arrhythmias.[197] To mitigate specific risks of arrhythmias associated with neostigmine, alternative routes of delivery via subcutaneous (SC), intramuscular (IM), and endonasal routes have been explored as options to reduce risks compared to intravenous (IV) administration.[198] Pyridostigmine is generally well-tolerated but can still produce cholinergic side effects.[199] Importantly, unlike neostigmine, pyridostigmine is less likely to cause heart block and life-threatening cardiac arrhythmias and thus can be safely administered without continuous cardiac monitoring.

Acetylcholinesterase inhibitors impact GI motility, hence their use in chronic constipation, pseudo-obstruction, abdominal distention, and dyspepsia.[197, 199-205] Neostigmine increases GI motility via increased ACh at the NMJ, increasing colonic transit and phasic pressure, reducing rectal compliance, and enhancing urgency.[206, 207] Neostigmine demonstrates efficacy throughout the GI tract and is more effective in reducing gastric residual volume than metoclopramide.[189] Additionally, it has been suggested to offer relief from symptoms of irritable bowel syndrome and leads to enhanced gas evacuation, propulsion and reduced abdominal bloating compared to placebo.[190] Neostigmine is a well-established treatment for ACPO, as discussed on page 30. Pyridostigmine, much like neostigmine, acts throughout the GI tract and acutely increases oesophageal contractility.[208] Moreover, in gastroparesis resulting from diabetes mellitus type 1 and autoimmune GI dysmotility, pyridostigmine alleviates GI symptoms and promotes gastric emptying.[209, 210] Pyridostigmine is also utilised for managing chronic constipation, reducing defecation and self-digitation time to alleviate constipation symptoms.[211] An RCT involving 30 patients demonstrated improved GI function in chronic constipation after six weeks whilst reporting

mild cholinergic side-effects.[212] In a retrospective cohort study of 13 individuals, pyridostigmine alleviated pseudo-obstruction symptoms, albeit did not effectively address slow transit constipation symptoms.[199]

1.8.1 ACETYLCHOLINESTERASE IN ANAESTHESIA

Neostigmine is commonly used as a reversal agent in anaesthesia to counteract the effect of non-depolarizing neuromuscular blocking drugs (NMBDs) used during surgery. NMBDs are administered to induce muscle paralysis, facilitating abdominal surgical procedures. However, before extubating a patient, the effect of NMBDs must be reversed to allow the patient to breathe independently.[213]

NMBDs are selected by the anaesthetist and come in multiple forms. Broadly, they are divided into depolarising NMBDs (e.g. succinylcholine) and nondepolarising NMBDs (e.g. rocuronium or vecuronium).[214] Depolarising NMBDs work by binding to postsynaptic cholinergic receptors, causing depolarisation, fasciculations and flaccid paralysis.[214] Succinylcholine is metabolised by pseudocholinesterase; thus, providing ACh reverses the action of NMBDs. Non-depolarising NMBDs are competitive ACh antagonists, thus block ACh binding at the motor end-plate.[192, 214, 215] They are further split into steroidal (e.g. rocuronium or vecuronium) or benzylisoquinoline (e.g. atracurium).[214]

Neostigmine competitively binds with acetylcholinesterase in the synaptic cleft of the neuromuscular junction (NMJ), increasing ACh concentration.[213 215] As a result, this reverses the action of NMBDs at the NMJ, enabling the patient to regain muscle function.[192, 215] However, if neostigmine is left unopposed, it can cause muscarinic side effects. Therefore, it is co-administered with an anticholinergic agent such as

glycopyrrolate to prevent these complications. Given the known motility effects of neostigmine, the impact this choice has on bowel motility is still being determined.[216-220]

Alternatively, sugammadex, a modified γ-cyclodextrin that encapsulates the aminosteroid NMBDs rocuronium and vecuronium with high affinity, may be used.[221] Sugammadex works independently of cholinergic pathways and, therefore, does not require co-administration of anticholinergic agents. Sugammadex mainly acts in the circulating plasma and does not readily enter the NMJ. Sugammadex rapidly chelates free NMBDs molecules in the plasma, establishing a concentration gradient encouraging the transfer of NMBDs from the NMJ into the plasma, where they are sequestered.[222] This decrease in available NMBDs at the NMJ leads to the reversal of the neuromuscular blockade. Importantly, unlike neostigmine, sugammadex does not possess the capacity to affect the CAIP.[223] Although sugammadex is not expected to affect the CAIP or cholinergic transmission, it is suggested it may alter GI motility and gastric emptying due to its affinity to bind with steroid hormones.[216, 217]

Several studies have compared the effects of neostigmine and sugammadex on GI recovery, with varied results.[216-218] In colorectal surgical patients carrying the most significant risk of POI, sugammadex led to an earlier return of bowel function.[219, 220] A recent meta-analysis (that includes Chapter 4 from our thesis) of five studies, including 1969 patients, showed sugammadex significantly reduced time to first stool and flatus compared to acetylcholinesterase inhibitors, showing no difference in complications and hospital stay.[224] Highlighted in this review, apart from the work in this thesis, previous studies do not compare neostigmine and sugammadex using a validated GI recovery outcome measure.

Neostigmine and sugammadex are used routinely in anaesthesia to counteract the effects of NMBDs. While neostigmine's effect on bowel motility is known, the choice of these agents on GI recovery is not yet fully understood.

1.8.2 ACETYLCHOLINESTERASE IN ACUTE COLONIC PSEUDO-OBSTRUCTION (ACPO)

Another common use for neostigmine is for treating ACPO, or Ogilvie's syndrome. It is a condition characterised by the sudden onset of colonic distension and the inability to pass stool or gas without an anatomic lesion that obstructs luminal content passage.[197, 225-228] It is a condition of older people and appears more common in males.[229] ACPO results secondary to paralysis of the colonic muscles, which results in various conditions. These are generally present in hospitalised patients such as trauma, infection, antipsychotics, electrolyte disruption and generally medically unwell patients such as Parkinson's disease.[197, 225-229] In surgery, ACPO may occur following spinal, caesarean or orthopaedic surgery most commonly.[229] The overt colonic distention can lead to ischemia or perforation, particularly of the caecum, and is potentially life-threatening.[197, 225-228]

ACPO can be treated with supportive care in patients without perforation or ischemia. Treating the predisposing condition, GI rest and decompression via colonoscopy are potential treatment options.[230-232] Additionally, patients may require neostigmine, which is highly effective in resolving ACPO.[197, 225-228, 233] In a meta-analysis including four randomised controlled trials (RCT), Valle et al. demonstrated that neostigmine effectively resolved ACPO (89.2% vs. 14.8%) without severe complications.[197, 225-228] ACIs reverse the colon's unbalanced sympathetic and parasympathetic activity, and increases colonic transit and phasic pressure, as well as reducing rectal compliance thus resolving

ACPO.[199, 206, 207] If these treatment approaches fail or in patients with ischemia or perforation, treating ACPO may necessitate surgical resection.[232]

Although there is good evidence for using neostigmine in ACPO, it does represent a different pathology from POI, which I explore further in our clinical review.

1.8.3 LIMITED DATA FOR ACETYLCHOLINESTERASE USE IN POSTOPERATIVE ILEUS

Current ERPs provide a variety of methods to improve recovery and GI recovery in patients.[166] One of the most common interventions is the use of laxatives, however, current uptake is very low in colorectal surgery.[234] With the STIMULAX trial, postoperative multimodal laxatives after elective colorectal surgery result in improved GI recovery and reduced incidence of POI.[235] However, there was limited improvement in complications and length of stay. I question whether further improvements can be achieved using ACIs.

The development of POI, as elaborated on page 8, is partially attributed to the CAIP mechanism. ACIs may influence this pathway by stimulating GI motility via nicotinic receptor activation and modulating the CAIP (Figure 1).

To further elaborate on the CAIP, neostigmine/pyridostigmine increases Ach availability, potentially influencing the α7nAChR. The effect of neostigmine on the CAIP via the α7nAChR has mainly been demonstrated in animal models. Recently summarised by Si et al., they showed neostigmine can reduce systemic inflammatory response to various septic and immunological stimuli.[144] Neostigmine has been shown to reduce IL-1 and TNF-a levels in rats following laparotomy and bowel perforation, as well as effectively minimising colitis in animal models.[236-238] Additionally, studies have demonstrated reduced

sepsis with neostigmine administration.[239-241] Reductions in inflammatory markers and neutrophil response have also been observed in animal models of allergies and asthma.[242-244] Despite these findings, until recently, there were limited studies examining the effectiveness of neostigmine in reducing sepsis.[245, 246] In the first double blinded RCT involving 50 patients with sepsis, neostigmine was found to significantly reduce sequential organ failure assessment (SOFA) scores, decrease the progression to septic shock and reduce vasopressor requirements.[246]

In studies related to GI patients, several RCTs have examined the efficacy of neostigmine and pyridostigmine to improve GI recovery postoperatively, with varied results. Chapter 4 will delve into these RCTs further. However, the existing evidence exhibits heterogeneity concerning dosage, route of administration, surgical procedures, and overall results. Remarkably, there needs to be more focus on the incidence of POI and validated measures of GI recovery.[25] Most studies are outdated, spanning many decades from 1986 to 2019, and primarily involve open surgical approaches not based in a modern ERP setting.[217, 247] Notably, there is a significant lack of data on patients undergoing colorectal surgery, the population at highest risk of POI in abdominal surgery.[17] Furthermore, adequately powered studies and comprehensive data on adverse events are absent.

In respect to pyridostigmine, there is only one RCT involving abdominal surgery.[248] The study examined 40 patients undergoing various abdominal operations, with pyridostigmine or placebo administered via an NG tube postoperatively. The intervention was commenced with patients with established POI. The results demonstrated a substantial increase in the proportion of patients given pyridostigmine passing stool compared to the placebo group in the first 24 hours (95% vs. 50%, p=0.001). Additionally, pyridostigmine resulted in a significant reduction in time to first flatus and time to first stool.[248] Moreover, this RCT has

limitations of a low sample size, including non-colorectal abdominal surgery (50% caesarean section) and sample bias. Colorectal operations were not included, and the routine use of NG tubes may have confounded the results. Unfortunately, safety data and complications were not reported.

This PhD builds upon an IDEAL phase 2B study exploring pyridostigmine to prevent POI.[249] In this study performed by our research group, fifteen patients were prescribed pyridostigmine postoperatively following colorectal surgery. There were no serious complications or treatment-related adverse events. Most postoperative complications were minor (12 out of 13, CD Grade $\leq$2). The findings indicated a rapid return of GI function, with a median time to GI-2 of 2 days (IQR 1-4) and three patients experienced POI.

A significant knowledge gap persists concerning the potential for pyridostigmine to enhance GI recovery and prevent POI, by modulating the CAIP, in colorectal surgical patients. A high-quality double blinded RCT is required to confidently advocate for pyridostigmine's inclusion in current ERPs.

1.9 SUMMARY

POI is a frequent complication following abdominal surgery, and its significant clinical and financial implications must be emphasised. However, the financial impact in the context of Australia and on a global scale needs to be further delineated. Furthermore, the uncharted territory of employing machine learning to explore additional risk factors for POI represents an exciting new avenue of research. However, identifying different risk factors and the financial implications of POI does not address the mechanism by which POI occurs. POI is partly mediated by activation of the CAIP yet remains unaddressed by current preventative strategies. While data on the utilisation of acetylcholinesterase inhibitors appears promising

to influence the CAIP and enhance GI recovery, ascertaining the efficacy of pyridostigmine after colorectal surgery as part of a regular ERP requires a sufficiently powered double blinded RCT.

1.10 AIMS

This thesis aims to provide evidence and conduct studies to fill the following gaps in the existing literature:

- Demonstrate the current evidence base for using ACIs following abdominal surgery.
- Explore the impact of ACIs on GI recovery when administered intraoperatively for neuromuscular reversal during anaesthesia.
- Delineate further the financial implications of POI.
- Provide high-quality evidence for using pyridostigmine following colorectal surgery as part of an ERP and the effect on the return of GI function.
- Investigate additional risk factors that can be targeted to reduce the incidence of POI.

1.11 PRECIS

The following chapters enhance the understanding of ACIs in abdominal surgery and elucidate the financial implications of POI. Furthermore, the research establishes the efficacy of pyridostigmine in enhancing GI function postoperatively and identifies potential risk factors and future strategies to improve GI recovery postoperatively.

Chapter 2 is a scoping review of the literature summarising the current applications of ACIs in abdominal surgery. The study investigates ACIs' effect on GI motility and discusses their potential use as part of an ERP to prevent or treat POI. The chapter also highlights the evidence for treating ACPO and its use as an anaesthetic agent to reverse neuromuscular blockade. **Chapter 3** delves further into the current basis of evidence, presenting the first systematic review of RCTs using ACIs to improve the return of GI function following abdominal surgery.

As highlighted in **Chapter 2**, neostigmine is frequently given during colorectal surgery for neuromuscular blockade reversal. **Chapter 4** provides our local experience in the form of a retrospective cohort study on the impact of neuromuscular reversal agents (sugammadex or neostigmine/glycopyrrolate) used during general anaesthesia on GI recovery, and is the first study to use a validated outcome measure.

To address an absence of Australian data and support the examination of the cost-effectiveness of preventative strategies for POI, **Chapter 5** reports the cost of POI after colorectal surgery in a single Australian public hospital, the Royal Adelaide Hospital. This retrospective cohort study focuses on complications and the associated impacts on the total cost of inpatient care. Given our findings, in **Chapter 6,** I broaden our perspective by performing the first systematic review and meta-analysis highlighting the global financial impact of POI following abdominal surgery on the total cost of inpatient stay.

Chapter 7 describes the main paper in this thesis. It outlines the design and results of the first double blinded RCT investigating the use of pyridostigmine as part of an ERP to improve GI function after colorectal surgery. This paper answers the knowledge gap

identified in the preceding chapters, providing high-quality evidence for using pyridostigmine for postoperative colorectal patients.

Following the main findings in this thesis, I examine future directions to improve GI recovery. **Chapter 8** evaluates machine learning techniques to identify new risk factors for POI to help guide preventive strategies. This technique identified sarcopenia as a potentially modifiable risk factor for POI.

The following chapters provide detailed analyses of the research findings and a discussion of the conclusions drawn and potential areas for future research.

CHAPTER 2: THE IMPACT OF ACETYLCHOLINESTERASE INHIBITORS ON ILEUS AND GUT MOTILITY FOLLOWING ABDOMINAL SURGERY: A CLINICAL REVIEW

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ANZ J Surg. 2021 Dec 19. https://doi.org/10.1111/ans.17418

Statement of Authorship

Title of Paper	The impact of acetylcholinesterase inhibitors on ileus and gut motility following abdominal surgery: a clinical review.
Publication Status	Published
Publication Details	Traeger L, Kroon HM, Bedrikovetski S, Moore JW, Sammour T. The impact of acetylcholinesterase inhibitors on ileus and gut motility following abdominal surgery: a clinical review. ANZ J Surg. 2022 Jan;92(1-2):69-76. https://doi.org/10.1111/ans.17418.

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Contribution to the Paper	Conceptualization; investigation; writing – original draft; writing – review and editing.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/10/2023

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Signature		Date	27/10/2023

This paper summarises the current application of ACIs in abdominal surgery. The scoping review summarises the effect of ACIs on gut motility and discusses their use in treating ACPO. Furthermore, I examine their role as an anaesthetic agent to reverse neuromuscular blockade and their potential inclusion in an ERP to prevent or treat POI.

2.1 ABSTRACT

Postoperative ileus is a common complication in the days following colorectal surgery occurring in up to 50% of patients. When prolonged, this complication results in significant morbidity and mortality, doubling the total costs of hospital stay. Postoperative ileus results from the prolonged inflammatory phase that is mediated in part by the cholinergic anti-inflammatory pathway. Acetylcholinesterase inhibitors, such as neostigmine and pyridostigmine, delay the degradation of acetylcholine at the synaptic cleft. This increase in acetylcholine has been shown to increase gut motility. They have been effective in the treatment of acute colonic pseudo-obstruction, but there is limited evidence for the use of these medications for reducing the incidence of postoperative ileus. This review was conducted to summarise the evidence of acetylcholinesterase inhibitors' effect on gut motility and discuss their potential use as part of an enhanced recovery protocols to prevent or treat postoperative ileus.

2.2 INTRODUCTION

With the advent of enhanced recovery protocols (ERPs), there has been renewed focus on research investigating improved recovery after surgery and reduction in postoperative hospital stay.[166] In colorectal surgery, postoperative ileus (POI) is a major cause of morbidity and prolonged hospital stay, leading to several novel therapies such as alvimopan, laxatives, prucalopride, vagal nerve stimulation, chewing gum and coffee to reduce its incidence with varying degrees of success.[146, 151, 153, 166, 235, 250] However, there are limited interventions that target one of the major pathophysiological pathway which results in POI, the cholinergic anti-inflammatory pathway (CAIP).[45, 146, 148, 151] Acetylcholinesterase inhibitors, such as neostigmine, are best known for treating acute colonic pseudo-obstruction (ACPO), and could act on this pathway. Given ACPO has distinct clinical features that differ from POI, this review will focus on the CAIP and discuss evidence, and potential application of, acetylcholinesterase inhibitors in surgical practice to prevent and/or treat POI.

2.3 METHODS

This paper is a synthesis of articles retrieved from an electronic database search of MEDLINE, EMBASE, Cochrane library, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCOhost) databases for papers prior to 11th March 2021. Keyword search terms of ‘surgery’, ‘colorectal’, ‘ileus’, ‘enhanced recovery’, ‘acetylcholinesterase inhibitor’, ‘pyridostigmine’ and ‘neostigmine’ were used. A total of 131 papers were selected for full text review. Papers were included if they were in English and investigated acetylcholinesterase inhibitors with a view to looking at anaesthetic, surgical and medical use. Given the broad application of acetylcholinesterase inhibitors in surgery, this data was prepared as a clinical review.

2.4 POSTOPERATIVE ILEUS (POI)

2.4.1 CLINICAL IMPACT

POI is a common complication typically detected two to four days after abdominal surgery, occurring in up to 50% of patients.[251] The principal features of POI include abdominal distention, intolerance of diet, nausea, vomiting and absent flatus or faeces.[128] Prolonged POI (PPOI), occurs in 10-25% of colorectal surgical patients, risking aspiration pneumonia, and the delay of nutrition predisposes to wound and anastomotic failure.[11, 45] Furthermore, POI increases end-organ dysfunction, increases 30-day mortality and prolongs hospital stay.[12] By preventing POI, a 33% reduction in delayed discharges, 20.7% fewer readmissions and 20% lower mortality rate could be achieved.[12] POI approximately doubles hospital admission costs, with some studies showing an increase by more than $US 8,000 per patient in hospital care.[12, 127]

2.4.2 RISK FACTORS

Previous research has identified male sex, chronic obstructive pulmonary disease and stoma formation as independent risk-factors for PPOI.[14, 63] Patients with all three factors carry a 38.3% chance of PPOI.[63] Other risk factors include increased age, previous abdominal surgery, emergency or prolonged operations, American Society of Anaesthesiologists physical status classification (ASA) score of ≥2, smoking history, increased perioperative transfusion, opioid use, preoperative hypoalbuminaemia, postoperative hypokalaemia, and anaemia.[14, 101]

2.4.3 PATHOPHYSIOLOGY

The development of POI is a two-phase response. The first phase is neurogenic and occurs during and immediately following surgical stimuli. Abdominal incision, peritoneal irritation and bowel manipulation activates a neuronal sympathetic response via splanchnic

and vagus nerves.[45, 252] The second phase is inflammatory, occurring approximately three hours postoperatively with a variable length of action. Activated macrophages in the intestinal muscularis secrete inflammatory mediators such as tumour necrosis factor alpha and interleukins 1β and 6.[24, 45, 63] This inflammatory phase has several contributing mechanisms, activating the CAIP, mediated by acetylcholine, could be one method of regulating this inflammatory cascade.[149] Increased levels of acetylcholine downregulate resident macrophages via the α7 nicotinic acetylcholine receptors (α7nAChR).[24, 45, 253] Acetylcholinesterase inhibitors increase acetylcholine availability potentially impacting the CAIP as well as stimulating gastrointestinal mass movement by activating the myenteric plexus, therefore could treat or prevent POI (Figure 2).

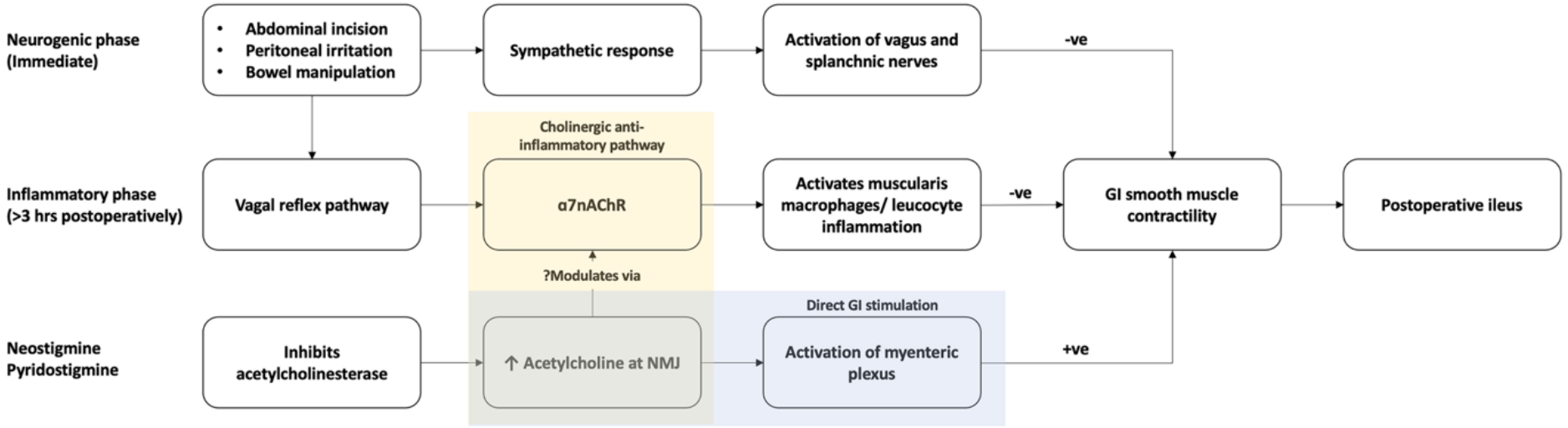

Figure 2. Acetylcholinesterase inhibitors impact on postoperative ileus.

GI, Gastrointestinal; NMJ, Neuromuscular junction.

2.4.4 POI VERSUS ACUTE COLONIC PSEUDO-OBSTRUCTION

POI refers to the impaired gastrointestinal transit after major abdominal surgery resulting from decreased peristaltic activity, without mechanical obstruction.[252] POI mainly impacts the small bowel. In contrast, acute colonic pseudo-obstruction (ACPO), also known as Ogilvie's Syndrome, is the impaired transit of colonic contents due to dysfunctional peristalsis of colon, resulting in dilatation.[252] ACPO commonly results from underlying cardiopulmonary, trauma or neurological disease, but can occur in non-abdominal surgery such as orthopaedic, cardiac or spinal surgery.[252] It is not often seen after abdominal surgery. In clinical practice, POI and ACPO are often used interchangeably however, this is not appropriate due to the distinct clinical features at presentation, and the different standard of care treatment paradigms.

2.5 ACETYLCHOLINESTERASE INHIBITORS

The main studies looking at the impact of acetylcholinesterase inhibitors on gut motility have investigated neostigmine and pyridostigmine, with the key differences shown in Table 1.

Table 1. Differences between neostigmine and pyridostigmine.

Adapted from [188]

	Neostigmine	**Pyridostigmine**
Brand names (international)	Prostigmin	Mestinon
Onset of action (min)	1	>16
Duration of action (min)	20-30	360
Elimination half-life (min)	77	113
Preparations	Intravenous/ intramuscular/ subcutaneous	Oral/ intravenous

2.5.1 NEOSTIGMINE

Neostigmine is an acetylcholinesterase inhibitor with a short onset of action (approximately 1 minute), duration of action of 20-30 minutes, and a half-life of 77 minutes when given intravenously (IV).[188] Neostigmine binds to the anionic site of acetylcholinesterase, and due to its slow hydrolysis, slows the degradation of acetylcholine.[188] The increased acetylcholine at the neuromuscular junction increases colonic transit and phasic pressure, ensuing a reduction in rectal compliance and enhances urgency.[206, 207] Neostigmine is associated with cholinergic side-effects such as abdominal pain, hypersalivation and vomiting. Neostigmine necessitates cardiac monitoring due to risk of bradycardia, heart block and life-threatening arrhythmias.[197] To decrease this risk, delivery via subcutaneous (SC), intramuscular (IM) and endonasal routes have been reported. In a 30-patient study of SC neostigmine, outcomes were similar to IV route, but without requirement for continuous cardiac monitoring.[198]

Neostigmine may be best known for its use in resolving ACPO. In a meta-analysis including four randomised controlled trials (RCT), Valle et al. demonstrated neostigmine was effective in 89.2% (84.6-95.2%) of patients versus 14.8% (0-45%) in the placebo group, without any serious complications.[197, 225-228] Fanaei et al. investigated IV neostigmine against placebo in ACPO post abdominal surgery. The mixed cohort of abdominal, spinal and orthopaedic patients demonstrated a 95% resolution in ACPO in the neostigmine group (n=42) and no clinical response with placebo.[225] A double blinded RCT by Van der Spoel et al., studied colonic ileus in critically ill medical patients.[226] IV neostigmine patients (11/13) passed stool with no response in the control group. These results were confirmed by Ponec et al. who showed a 91% prompt evacuation of flatus or stool following administration of IV neostigmine in a RCT.[227] Another cohort study of mixed surgical and medical patients also demonstrated an 86% relief of ACPO following IV neostigmine.[233] Repeat dosages of

neostigmine have also been shown to resolve ACPO. A prospective study in 11 patients, showed the majority of patients decompressed following the first dose (8/11), while an additional two resolved after a second dose.[254]

2.5.2 NEOSTIGMINE FOR POI

Neostigmine is effective throughout the gastrointestinal tract and is more effective in reducing gastric residual volume than metoclopramide.[189] It also reduces symptoms of irritable bowel syndrome and when compared to placebo, results in greater gas evacuation and propulsion and improved abdominal bloating.[190]

Several studies have investigated the impact of neostigmine on POI. A 2008 Cochrane review into the use of prokinetics to prevent POI, reported insufficient evidence to incorporate neostigmine in POI prevention.[255] A double blinded RCT compared IM neostigmine to a placebo in patients following laparotomy who had POI lasting greater than two days. They found no clinical difference in POI rates (n=90).[256] Orlando et al. investigated endonasal delivered neostigmine demonstrating a small reduction in flatus time compared to placebo in a post-laparotomy RCT (ratio of means 0.57 (95% CI 0.33,1.01)).[228] A retrospective study of SC neostigmine comprised of spinal and colorectal patients, demonstrated safe usage of neostigmine in POI (n=152), ACPO (n=20) and constipation (n=10), with a median time to first bowel movement of 29.19 hrs (IQR 12.18-56.84; n=182). Two patients became bradycardic (1.29%), and another had an anastomotic leak (0.55%), although this was not conclusively linked to neostigmine.[257] By including both ACPO and POI patients together, this adds further evidence that neostigmine can be considered for use in both diagnoses.

Several RCTs have also investigated neostigmine after cholecystectomy and abdominal aortic surgery. In a five-arm RCT of open cholecystectomy with intra-mesenteric bupivacaine injections and/or SC neostigmine was compared to laparoscopic cholecystectomy (n=100). The study demonstrated no POI in the laparoscopic group. When comparing neostigmine and bupivacaine within open cholecystectomy there was a reduction in time to first stool (56 (24-96) vs 96 (60-125) hrs, $p<0.001$).[258] Hallerback et al. undertook another RCT in open cholecystectomy patients receiving either placebo, SC neostigmine or SC neostigmine with IV propranolol (n=51). The results of this study showed reduced time to passage of stool in the propranolol and neostigmine group (68±6 vs 90±7 hrs, $p<0.01$), mainly in patients over 60 years old.[259] Furthermore, in a study of elective open abdominal aortic surgery for aneurismal or occlusive disease which patients received either a neostigmine thoracic epidural or placebo, there was no increase in complications in the neostigmine group while these patients had a decreased time to restoration of bowel sounds and flatus, but no change in time to first stool.[196]

Overall, neostigmine has some positive effects in reducing POI after abdominal surgery. With ERPs favouring minimally invasive surgery, the existing evidence is insufficient to support neostigmine's impact on laparoscopic surgery. There is also a lack of colorectal specific studies. A summary of these studies in found in Table 2.

Table 2. Acetylcholinesterase inhibitor acute colonic pseudo-obstruction (ACPO)/ postoperative ileus (POI) studies.

Study	Design	No. patients	Emergency / Elective	ACPO/ POI	Cohort (medical/ surgical)	Intervention	Primary outcome	Result	Complications
Neostigmine									
Fanaei et al. 2008[225]	RCT	42 (21 each arm)	NA	ACPO	Surgical – laparoscopic cholecystectomy / appendicectomy, joint replacement, prostatectomy, laminectomy.	IV, 2.5 mg neostigmine, over ½ hour	Passage of flatus and stools	Neostigmine - 95.23% Placebo - 0%	5 mild abdominal cramping, 4 moderate-severe cramping, 8 hypersalivation, 4 vomiting, 1 bradycardia requiring atropine
Caliskan et al. 2008[196]	RCT	45 (18 neostigmine, 16 placebo after exclusions)	Elective	POI	Surgical - open abdominal aortic	Epidural, 1 mg/kg neostigmine + 20 ml bupivacaine 0.5%, stat	Time to flatus, bowel sounds or defaecation (hours, mean)	Bowel sound Neostigmine - 11±11 Placebo - 22±12* Flatus Neostigmine - 21±15 Placebo - 36±19* Defecation Neostigmine - 58±41 Placebo - 75±48	Neostigmine – 2 arrhythmia, 1 respiratory failure 1 renal failure. Placebo – 1 respiratory failure.
Orlando et al. 1994 [228]	RCT	40 (20 each arm)	Emergency (n=20) Elective (n=20)	POI	Surgical – OC and emergency intra-abdominal	Inhaled, neostigmine 5.4 mg/puff, ≤6 puff/day until 4th day	Time to passage of first flatus or stool (ratio of means)	0.57 (95% CI 0.33, 1.01)	Asthenia in all patients. Neostigmine – 1 miosis with diaphoresis
García-Caballero et al. 1993 [258]	RCT	100 (20 each arm)	Elective	POI	Surgical – 1. OC 2. OC + bupivacaine	IV, neostigmine 0.5 mg + IV propranolol	Time to gas, time to faeces (hours,	Gas 1. 60 (24-90) 2. 48 (24-96) 3. 48 (45-72)	Group 3 – 3 bradycardia/ hypotension

					3. OC + neostigmine + propranolol, 4. OC +bupivacaine + neostigmine +propranolol 5. Laparoscopic cholecystectomy	7.5 mg intra mesenteric ± bupivacaine 0.5% 20 ml	median, range)	4. 39 (24-69)* 5. 10 (8-14)* <u>Faeces</u> 1. 96 (60-125) 2. 72 (36-120)* 3. 96 (45-125) 4. 56 (24-96)* 5. 36 (24-40)*	<u>Group 4</u> – 1 anxiety
Myrhoj et al. 1988 [256]	RCT	90 (42 each arm after exclusions)	NA	POI	Surgical – Gastric, pancreatic biliary, intestinal	IM, neostigmine 0.5 mg, 3 hourly from 3rd day	Passage of flatus or stool movement (%, range)	Neostigmine - 19% (9-34%) Placebo - 34% (20-50%)	Nil reported
Hallerback et al. 1987 [259]	RCT	62 (18 neostigmine, 16 propranolol + neostigmine, 17 placebo after exclusions)	Elective	POI	Surgical – OC	SC, neostigmine 0.5 mg + IV propranolol 10 mg, BD	First passage of stool (hours, mean)	Neostigmine - 82±6** Neostigmine+ propranolol - 68±6** Placebo - 90±7**	1 neostigmine allergy
Ponec et al. 1999[227]	RCT	21 (11 neostigmine, 10 placebo)	NA	ACPO	Surgical and Medical	IV, neostigmine 2 mg, stat	Immediate clinical response (%)	Neostigmine – 91% Placebo - 0%	Neostigmine - 9 mild cramping, 8 excessive salivation, 2 vomited, 2 bradycardia requiring atropine, 1 syncope.
Van der Spoel et al. 2001[27]	RCT	24 (13 neostigmine, 11 placebo)	NA	ACPO	Medical and Surgical (cardiothoracic, vascular)	IV, neostigmine 5 mg, stat + 8 hours if no clinical response	Defecation within 24 hours (%)	Neostigmine – 79% Placebo – 0%	Neostigmine – 3 excessive salivation.

Kram et al. 2018 [257]	Multi-centre retrospective observational	182 (155 surgical, 27 medical)	NA	POI, ACPO, constipation	Surgical- orthopaedic, colorectal, cardiothoracic, neuro and urology Medical	SC, neostigmine 0.2 mg – 1 mg, OD – QID	First bowel motion (hours, median, IQR)	Cohort -29.19 (12.18 - 56.84) Surgical - 26.97 (9.58-57) Medical - 29.19 (21.7-59.92)	21 nausea, 2 bradycardia, 1 diarrhea, 1 anastomotic leak
Trevisani et al 2000 [233]	Prospective	28 (21 medical, 7 surgical)	NA	ACPO	Mixed	IV, neostigmine 2.5 mg stat	Colonic decompression and return of normal bowel function (%)	Complete resolution - 93% Immediate relief -86%	Abdominal cramps, nausea, light headedness
Paran et al 2000 [254]	Prospective	11 (7 surgical, 4 medical)	NA	ACPO	Surgical – orthopaedic, trauma, spine, obstetrics Medical	IV, neostigmine 2.5 mg, stat	Response to intervention (%)	Resolution – 82% Partial - 9% No effect – 9%	1 mild abdominal cramp
Pyridostigmine									
Malekneja d et al. 2018 [248]	RCT	40 (20 each arm)	Emergency	POI	Surgery – caesarean section, cholecystectomy , appendicectomy, antrectomy	NG, pyridostigmine 60 mg BD, commenced after 3 days	Passage of gas and stool (hours, mean)	<u>Gas</u> Pyridostigmine - 5.4±4.7 Placebo - 32.4±9.9 <u>Stool</u> Pyridostigmine - 4.9±3.4 Placebo - 36.2±10.3 ***	Nil reported
Dudi-Venkata et al 2021[249]	Phase II safety	15	Elective	POI	Surgery – Colorectal	PO, pyridostigmine 60 mg BD from 6 hours postoperatively till first stool	Return of gastrointestinal function measured by GI-2 (days, median)	2 (1-4)	3 diarrhea 1 atrial bigeminy

BD, twice daily; IM, intramuscular; IV, intravenous; NA, not available; NG, Nasogastric; OC, open cholecystectomy; *, p value < 0.05; **, p value <0.01; ***, p value <0.001; RCT, Randomised controlled trial; SC, subcutaneous.

In anaesthesia, neostigmine is used to reverse the effects of non-depolarizing neuromuscular blocking agents used during surgery. Several studies have investigated neostigmine's effect on postoperative gastrointestinal motility. Most of these studies compare neostigmine against sugammadex, a selective rocuronium or vecuronium binder, with varied results. Sugammadex has affinity to bind with steroid hormones, thus it is thought to theoretically increase gastric emptying and gut motility.[217] Sen et al., performed an RCT in thyroidectomy patients, demonstrating a faster time to bowel motion with neostigmine compared to sugammadex (24 [IQR10-48] vs. 32 hrs [12-72]; n=72).[216] Alternatively, studies report favourable effect for the use of sugammadex over neostigmine for decreased POI. In the largest study of over 8000 intraperitoneal surgical patients, sugammadex resulted in a faster return to time of first stool (Hazard ratio 1.27 (1.12-1.43), 95% CI, p<0.001).[218] This likely reflects that neostigmine is administered with an anticholinergic (commonly glycopyrrolate) to counteract it's cholinergic effects, thus negating the effects on gastrointestinal motility. As sugammadex has no direct cholinergic activity, this may account for the differences in gastrointestinal recovery. Given sugammadex cannot be administered in the postoperative phase, further study should investigate acetylcholinesterase inhibitors in the prevention and treatment of POI.

2.5.3 PYRIDOSTIGMINE

Pyridostigmine is an analogue of neostigmine with one quarter of the potency. It binds to acetylcholinesterase via a covalent bond and is lipid insoluble. Its onset time is >16 mins, duration of action is 6 hours and half-life of 177 minutes when delivered orally.[188] Since the 1950s, pyridostigmine has been used to treat Myasthenia Gravis, an autoimmune disease with autoantibodies against the nicotinic acetylcholine receptor.[193] Pyridostigmine binds with acetylcholinesterase, delaying the hydrolysis of acetylcholine, enabling more time for

acetylcholine to interact with the defective receptor, allowing short-term relief of the symptoms of Myasthenia Gravis.[188, 193]

Pyridostigmine is commonly used in chronic constipation and decreases time to defecation and self-digitation to resolve constipation.[211] Bharucha et al. performed an RCT showing improved bowel function in chronic constipation after six weeks, with mild cholinergic side-effects (n=30)[212], and in a retrospective cohort study pyridostigmine reduced pseudo-obstruction symptoms, but failed to reduce slow transit constipation symptoms (n=13).[199]

Pyridostigmine is well-tolerated, however can cause cholinergic side-effects like headaches, bloating and hypersalivation.[199] Diaphoresis, abdominal cramps, pre-syncope, muscle fasciculations, fatigue, nausea, urinary urgency, bronchial secretions, rash, blurred vision and bradycardia have also been reported.[193-196] Unlike neostigmine, heart block and life-threatening cardiac arrhythmias are less likely thus pyridostigmine can be safely administered without cardiac monitoring.

2.5.4 PYRIDOSTIGMINE FOR POI

Pyridostigmine, like neostigmine, acts throughout the gastrointestinal tract. It acutely increases oesophageal contractility[208] and in conditions with associated gastroparesis, such as diabetes mellitus type 1 and autoimmune gastrointestinal dysmotility, pyridostigmine reduces gastrointestinal symptoms and increases gastric emptying.[209, 210]

The largest RCT looking at pyridostigmine for POI treatment, included 40 patients undergoing various abdominal operations. Pyridostigmine or a placebo was given via a nasogastric tube postoperatively. In the first 24 hours, more patients given pyridostigmine passed stool compared to the placebo group (95% vs. 50%, p=0.001). However, given the

low sample size, this study was underpowered.[248] This study had a greater proportion of caesarean section patients, and limitations of sample bias. In addition, colorectal operations that have the highest incidence of POI were not included, and the routine use of nasogastric tubes likely confounded the results (as this is not standard practice in the types of surgery included in the study). Unfortunately, safety data and complications were not reported. In our own experience, we have safely administered pyridostigmine in a phase 2 study to prevent POI in 15 colorectal patients. There were no adverse effects with a time to stool and toleration of solid diet of two days (IQR 1-4).[249]

2.6 DISCUSSION

POI is a significant complication, increasing morbidity and length of stay, particularly following colorectal surgery.[11, 12, 45] With modern ERPs, methods of reducing length of stay have been investigated, such as laxatives and alvimopam.[235, 250] Although these strategies have been shown to impact gut motility and POI, there are limited strategies that target the CAIP, a significant pathway in the development of POI.[146, 148, 151]

Our review has identified the effects acetylcholinesterase inhibitors have on gastrointestinal motility, and the potential to impact the CAIP. While more evidence exists for the use of neostigmine to treat POI, there is a lack of well-powered studies, especially for patients undergoing colorectal surgery who have highest rates of POI.

Future research of novel therapies targeting the CAIP is required. Pyridostigmine appears to have a similar effect on gut motility to neostigmine, however has the benefit of being an oral preparation, with a reduced risk of cardiac arrhythmias and therefore does not require cardiac monitoring. We speculate that pyridostigmine may modulate the CAIP and stimulate gastrointestinal motility. Given there are no colorectal surgical studies investigating

pyridostigmine's impact on POI in an ERP, there is a significant gap in the literature. We are now recruiting for a double blinded RCT to investigate this question (at https://www.anzctr.org.au/ ACTRN12621000530820).

This paper was limited to a clinical review, due to the broad application of acetylcholinesterase inhibitors in surgery. The available papers varied in the definitions of POI, were not based in modern ERPs, mixed surgical indications, approaches, techniques and were published over many decades. Given the lack of heterogeneity and available evidence the data was presented through a clinical review.

2.7 CONCLUSION

POI is common following abdominal surgery, resulting in significant morbidity and mortality. The prolonged inflammatory phase of POI is mediated by activation of the CAIP. Despite the historic data on the use of neostigmine in ACPO and POI, due to the associated risk of adverse effects, a sufficiently powered RCT with pyridostigmine embedded in an ERP is required to confirm the efficacy after colorectal surgery.

CHAPTER 3: USE OF ACETYLCHOLINESTERASE INHIBITORS IN REDUCING TIME TO GASTROINTESTINAL FUNCTION RECOVERY FOLLOWING ABDOMINAL SURGERY: A SYSTEMATIC REVIEW.

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Dig Surg. 2023. https://doi.org/10.1159/000535753

Statement of Authorship

Title of Paper	Use of acetylcholinesterase inhibitors in reducing time to gastrointestinal function recovery following abdominal surgery: A systematic review.
Publication Status	Published
Publication Details	Traeger L, Dudi-Venkata N, Bedrikovetski S, Kroon H, Moore JW, Sammour T. Use of acetylcholinesterase inhibitors in reducing time to gastrointestinal function recovery following abdominal surgery: A systematic review. Dig Surg. 2023.

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Contribution to the Paper	Conceptualization; Methodology; Investigation; Writing – Original Draft; Writing – Review & Editing.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/10/2023

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Contribution to the Paper	Investigation; Writing – Original Draft; Writing – Review & Editing.		
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Contribution to the Paper	Writing – Original Draft; Writing – Review & Editing; Supervision.		
Signature		Date	27/10/2023

This systematic review is the first to examine the use of ACIs to accelerate the recovery of GI function. This paper investigates RCTs, evaluating the methodology and results. The findings of this review provide the foundation for this thesis, highlighting the need for a double blinded RCT using pyridostigmine to enhance GI recovery after colorectal surgery.

3.1 ABSTRACT

Purpose: Postoperative ileus (POI) is a significant complication following abdominal surgery, increasing morbidity and mortality. The cholinergic anti-inflammatory response is one of the major pathways involved in developing POI, but current recommendations to prevent POI do not target this. This review aims to summarise evidence for the use of acetylcholinesterase inhibitors, neostigmine and pyridostigmine, to reduce the time to return of gastrointestinal function (GI) following abdominal surgery.

Methods: A systematic search of various databases was performed from 1946 to May 2023. Randomised controlled trials (RCT) on acetylcholinesterase inhibitors in intra-abdominal surgery were included. Data on time to flatus and/or stool and side effects were extracted.

Results: Among 776 screened manuscripts, 8 RCTs (703 patients) investigating acetylcholinesterase inhibitors, in intra-abdominal surgery were analysed. Five studies showed a significant reduction in time to flatus and/or stool by 17-47.6 hours. Methodological variations, differing procedure types, and potential bias were observed. Limited studies reported side effects or length of stay.

Conclusion: Acetylcholinesterase inhibitors may reduce the time for gastrointestinal function to return. However, current evidence is limited and biased. Further studies incorporating acetylcholinesterase inhibitors in an enhanced recovery protocol are required to address this question, especially for patients undergoing colorectal surgery.

3.2 INTRODUCTION

Postoperative ileus (POI) is the delay in return of gastrointestinal function following abdominal surgery, occurring in up to 30% of patients.[17, 128] This complication is characterised by intolerance of oral diet and absence of flatus and stool, meaning that patients with POI suffer from vomiting, predisposing them to malnutrition, delayed wound healing, anastomotic leak, and pneumonia.[12, 128] As a result, patient recovery is negatively impacted, significantly increasing length of stay and inpatient stay costs.[29, 126, 127, 260, 261]

The mechanism of POI can be described as a two-phase process. The initial, neurogenic phase occurs during surgery as a response to surgical stimuli.[45] The secondary, inflammatory phase begins around three hours postoperatively, with the release of inflammatory mediators affecting bowel function for a varied length of time.[45, 63] This inflammatory cascade is mediated, in part, by the cholinergic anti-inflammatory pathway (CAIP).[149, 262, 263]

To reduce the negative impact of POI, research has focused on improving surgical recovery and reducing postoperative hospital stay as part of enhanced recovery protocols (ERPs).[166] Several novel therapies such as alvimopan, methylnaltrexone, prucalopride and trials using laxatives, chewing gum, and coffee have been investigated with varying degrees of success.[146, 153, 166, 235, 250, 264] However, limited ERP strategies target the CAIP.[45, 146, 148, 151] This is despite acetylcholinesterase inhibitors, such as neostigmine and pyridostigmine, being readily available and having their direct mechanism of action via this pathway. In abdominal surgery, these drugs are mostly known for treating acute colonic pseudo-obstruction (ACPO) by stimulating gastrointestinal mass movement.[227] While they have also been suggested for use in reducing the time to return of gastrointestinal function, evidence for their use remains sparse, as highlighted in our previous scoping

clinical review.[196, 256, 258, 259, 265, 266] Previous studies have variability in the subspecialty, do not reside within modern ERPs or laparoscopic surgery, and are not colorectal specific where POI is most common.[196, 249, 256, 258, 259, 265, 266] Therefore, our focus of this systematic review was to establish the evidence base, namely randomised controlled trials (RCTs), for the use of acetylcholinesterase inhibitors in abdominal surgery to reduce the time to return of gastrointestinal function.

3.3 METHODS

This study was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021250387). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[267] guidelines were used for conducting and reporting the results of this study (Appendix A).

3.3.1 SEARCH STRATEGY

Two independent reviewers (LT and NNDV) performed a systematic search of PubMed (1956-2023), OVID MEDLINE (1946-2023), EMBASE (1974-2023), Cochrane Library (2005-2023), Clinical trials.gov, and Cumulative Index of Nursing and Allied Health Literature (CIANHL) databases (1984-2023). Studies were included until the 31st May 2023. Medical subject headings (MeSH) and keyword search terms related to ‘acetylcholinesterase inhibitors’, ‘neostigmine’, ‘pyridostigmine’, ‘abdominal’, ‘surgery’, ‘postoperative’, ‘gut motility’ and ‘ileus’ were used. The search strategies are provided in (Appendix A).

3.3.2 ELIGIBILITY CRITERIA

Studies were included for full-text review if they were related to POI or gut motility following surgery. The articles needed to be available in full-text and published in English. Inclusion

criteria were RCTs, human patients over 18 years of age undergoing elective or emergency abdominal surgery, diagnosed with POI, investigating bowel function, and given acetylcholinesterase inhibitors as an intervention. As a limited number of papers were identified on preliminary screening, all intra-abdominal surgical cases at risk of POI were included. Articles were excluded if POI resulted from mechanical obstruction or the study related to ACPO. Due to the primary outcome being identified, non-randomised controlled trials, prospective and retrospective cohort studies, case-control and cross-sectional studies were excluded.

3.3.3 STUDY SELECTION

Studies were selected using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Both reviewers individually screened titles and abstracts. Full-text review was performed with the references checked to identify potential additional articles. Any disagreements were resolved by consensus, arbitrated by a third author (SB).

3.3.4 DATA EXTRACTION AND SYNTHESIS

Two reviewers (LT and NNDV) extracted the data independently using a predefined standard data extraction form. Extracted baseline data included author name, country, year, patient population, surgery type, number of patients, drug route, and type of intervention. The primary outcomes extracted included time to passage of first stool and flatus. Secondary outcomes that were extracted included side effects and length of stay. Data were corroborated following extraction and any discrepancies in the extracted data were resolved by the third reviewer (SB).

3.3.5 RISK OF BIAS IN INDIVIDUAL STUDIES

Risk of bias was recorded using the Cochrane risk-of-bias for randomised trials (RoB 2)[268] and was tabulated using ROBVIS.[269]

3.3.6 STATISTICAL ANALYSIS

Data were analysed using descriptive statistics and presented as time in hours, frequency and percentages as appropriate. Due to the mixture of median (range), median (IQR) and mean (SD), the differences in patient population, and type of surgery, the results of the studies were unable to be pooled into a meta-analysis.

3.4 RESULTS

The literature search identified 776 studies, of which 167 were duplicates and were removed. Of the 609 studies, 588 were excluded after they did not meet the predefined inclusion criteria on screening the title and abstract. Twenty studies were screened in full-text review, with eight meeting the inclusion criteria (Figure 3).[196, 217, 247, 248, 256, 258, 259, 265]

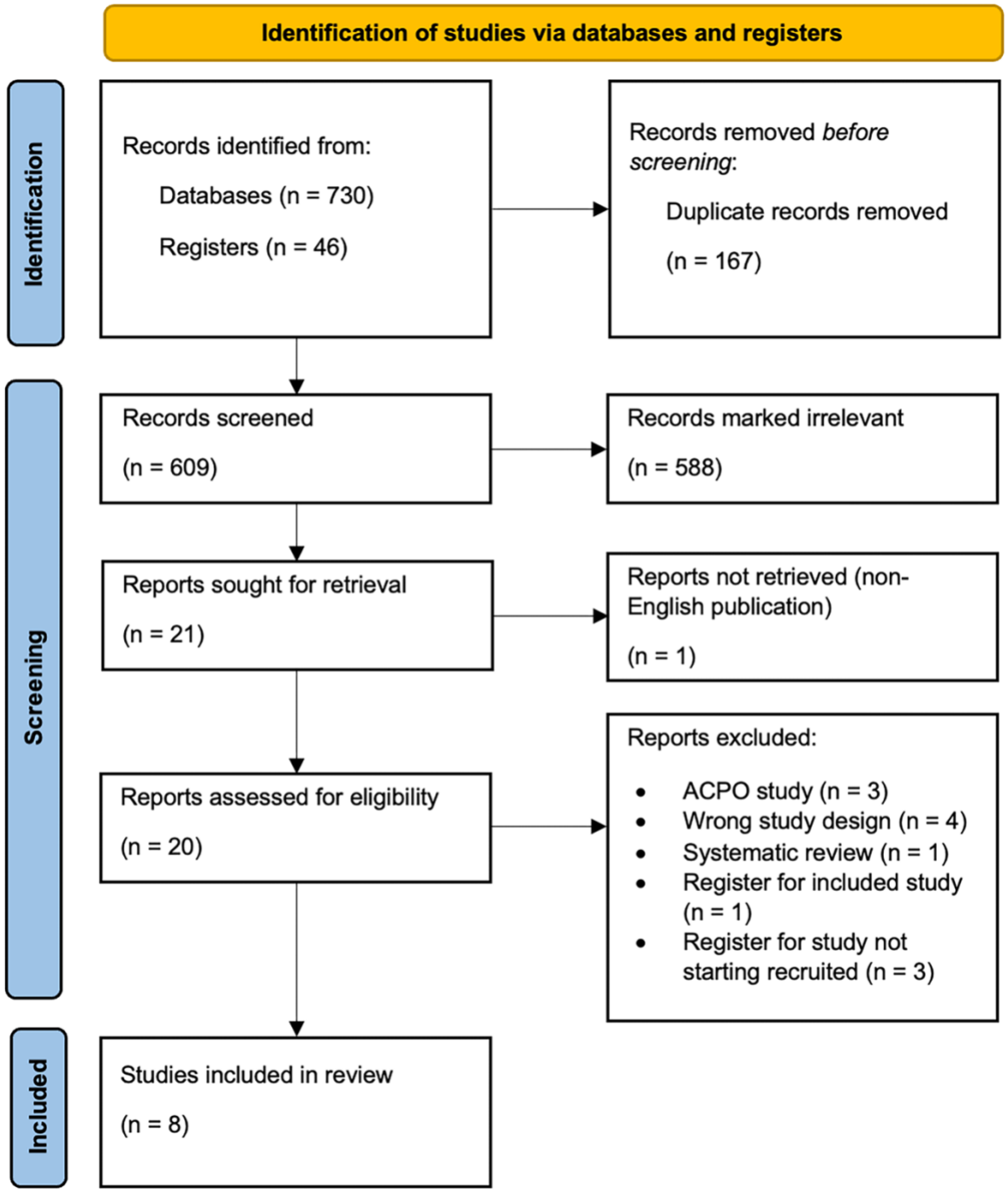

Figure 3: PRISMA flow chart.

3.4.1 CHARACTERISTICS OF STUDIES

The eight included RCTs spanned seven countries and were published between 1986 and 2019, including 703 patients. There was heterogeneity in surgery types ranging from general surgery, gynaecology and vascular, and a mix of laparoscopic and open cases. Five studies were double blinded randomised controlled trials[196, 217, 256, 259, 265], of which three provided power calculations for recruitment targets.[196, 217, 256] Three studies were single-blinded[247, 248, 258], with one of these studies blinding only the participants.[248] Of the eight studies, only three were embedded in a standard enhanced recovery protocol.[196, 217, 247] The full study characteristics are provided in Table 3.

Table 3. Characteristics of included studies.

Reference	Country	Year	Operations	Surgical approach	No. of Patients			Intervention	Route of Administration	Blinding
					Intervention	Control	Total			
An et al.[217]	Korea	2019	Cholecystectomy	LAP	53	49	102	Pyridostigmine	IV	Double
Caliskan et al.[196]	Turkey	2008	Abdominal aortic surgery	Open	18	16	34	Neostigmine	Thoracic epidural	Double
Garcia – Caballero et al.[258]	Spain	1993	Cholecystectomy	Open/ LAP	76	20	96	Neostigmine + propranolol ± bupivacaine	SC	Single (Patients)
Hallerback et al.[259]	Sweden	1987	Cholecystectomy	Open	34	17	51	Neostigmine ± propranolol	SC	Double
Madsen et al.[265]	Denmark	1986	Gastric, pancreatic, intestinal	Open	24	24	48	Neostigmine	IM	Double
Maleknejad et al.[248]	Iran	2018	Gynaecological, gastric, bowel	-	20	20	40	Pyridostigmine	NG	Single (Patients)
Myrhoj et al.[256]	Denmark	1988	Gastric, pancreatic, intestinal	Open	42	44	86	Neostigmine	IM	Double
You et al.[247]	China	2018	Gastrectomy	Open/ LAP	193	53	246	Neostigmine	Acupoint or IM	Single (Investigators)

IM, Intramuscular; IV, Intravenous; LAP, Laparoscopic; NG, Nasogastric; SC, Subcutaneous

3.4.2 INTERVENTIONS

The studies used several routes of administration, dosing, and type of acetylcholinesterase inhibitors. The route of administration of the acetylcholinesterase inhibitor also differed between studies and included two subcutaneous (SC)[258, 259], one intravenous (IV)[217], one thoracic epidural[196], one nasogastric (NG)[248], two intramuscular (IM)[256, 265] and one acupoint (acupuncture site injection) and IM administration.[247] Six studies gave the control drug via the same route.[196, 217, 248, 256, 259, 265] Two studies compared intervention to standard therapy.[247, 258]

Six studies used neostigmine as intervention[196, 247, 256, 258, 259, 265] and two used pyridostigmine.[217, 248] The six studies investigating neostigmine differed in terms of intervention, control and timing of administration. Caliskan et al. compared a neostigmine epidural against a placebo given at the end of surgery and 8 hours postoperatively in abdominal aortic surgery.[196] Two studies compared SC neostigmine following cholecystectomy, given until the first stool.[258, 259] The other three studies gave IM neostigmine with one of them also giving neostigmine via acupoint injection postoperatively.[247, 256, 265] Myrhoj et al. gave three IM doses of neostigmine over one day following laparotomy for gastric, pancreatic and intestinal surgery.[256] Whereas Madsen et al. gave three IM neostigmine doses, three days following a laparotomy for gastric, pancreatic and intestinal surgery.[265] You et al. gave neostigmine via acupoint and IM injections following gastrectomy until first bowel action.[247]

The two studies investigating pyridostigmine also demonstrated variability in timing and type of intervention. An et al. studied IV pyridostigmine against sugammadex to reverse neuromuscular blockade following laparoscopic cholecystectomy and its effect on gastrointestinal recovery.[217] Maleknejad et al. gave oral pyridostigmine via NG three days

after the development of POI and compared this to a placebo.[248] The interventions in the selected trials are summarised in Table 4.

Table 4. Summary of study interventions and outcomes related to gastrointestinal function.

Reference	Intervention	Control	Timing of intervention	Primary outcome	Secondary outcome
An et al.[217]	Pyridostigmine 0.2 mg/kg + glycopyrrolate 0.008 mg/kg IV	Sugammade x 2 mg/kg IV stat	Intraoperative	Time to first passage of flatus and defecation	Stool type
Caliskan et al.[196]	Neostigmine 5ml (1 mcg/kg) epidural	Placebo	End of surgery and 8 hours postoperatively	Time to flatus and defection	Length of hospital stay Postoperative complications
Garcia – Caballero et al.[258]	(1) Open cholecystectomy + intraoperative bupivacaine 20ml 0.5% (2) Open cholecystectomy + Neostigmine 0.5mg SC BD + Propranolol 7.5mg Q8H IV (3) Both 1+2 (4) Laparoscopic cholecystectomy	Open cholecystectomy with no intervention	Intraoperatively and postoperatively until first stool	Time to passage of first flatus and stool	Adverse effects
Hallerback et al.[259]	Neostigmine 0.5mg SC BD and/or Propranolol 10mg IV	Placebo	Postoperatively until first stool	Time to passage of first stool	Adverse effects
Madsen et al.[265]	Neostigmine 5 mcg/kg IM	Ceruletide	Postoperatively from day 3, every 3 hours until passage of flatus or stool or 3 injections.	Passage of flatus or stool (%)	-
Maleknejad et al.[248]	Pyridostigmine 60mg NG BD	Placebo	Postoperatively from day 3	Time to passage of flatus and stool	Frequency of response
Myrhoj et al.[256]	Neostigmine 0.5mg IM	Placebo	Postoperative for 3 doses	Passage of flatus or stool (%)	-
You et al.[247]	(1) ST 36 acupuncture OD (2) ST36 acupoint neostigmine injection 0.5mg OD (3) Neostigmine IM 0.5mg OD	Standard therapy	Postoperative until bowel recovery	Time to first flatus, first defecation	Drug related adverse events

BD: twice daily; IM: intramuscular; IV: Intravenous; kg: kilogram; mcg: microgram; mg: milligram; ml: millilitre; NG: nasogastric; OD: once daily; Q8H: 8 hourly; SC: subcutaneous.

3.4.3 ASSESSMENT OF RISK OF BIAS

An et al. had low risk of bias, due to a robust methodology.[217] Six studies were considered to have concerns for risk of bias.[196, 247, 256, 258, 259, 265] This related to concerns about bias of reported results, often missing adverse effects and results. One study, Maleknejad et al., had a high risk of bias with potential for deviations in measured outcomes.[248] These data are presented in a summary and traffic light plot, Figure 4 and Figure 5 respectively.

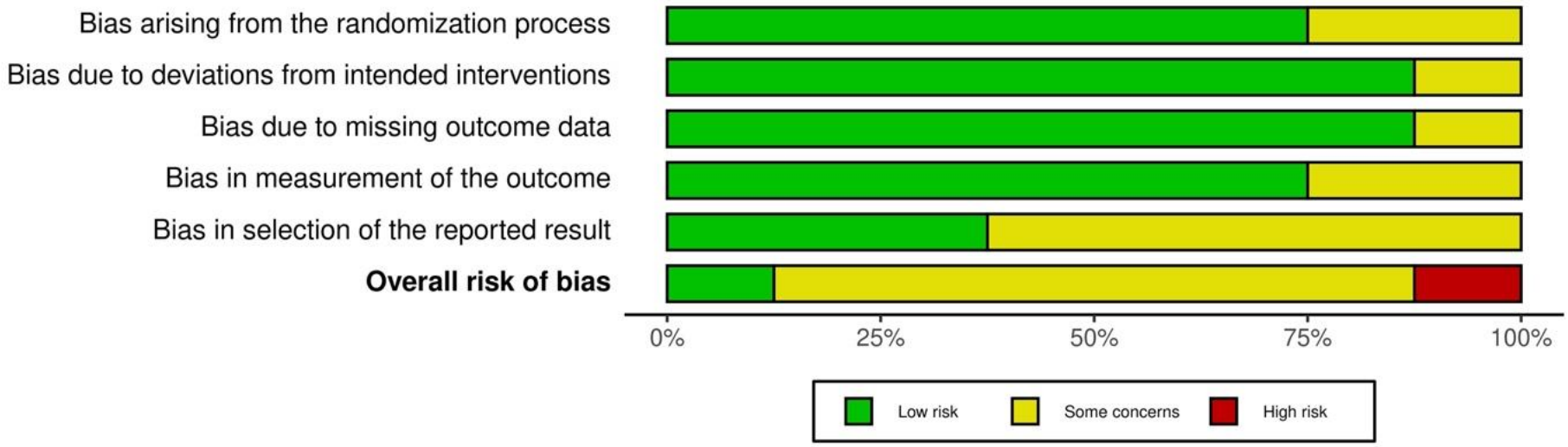

Figure 4. Summary plot.

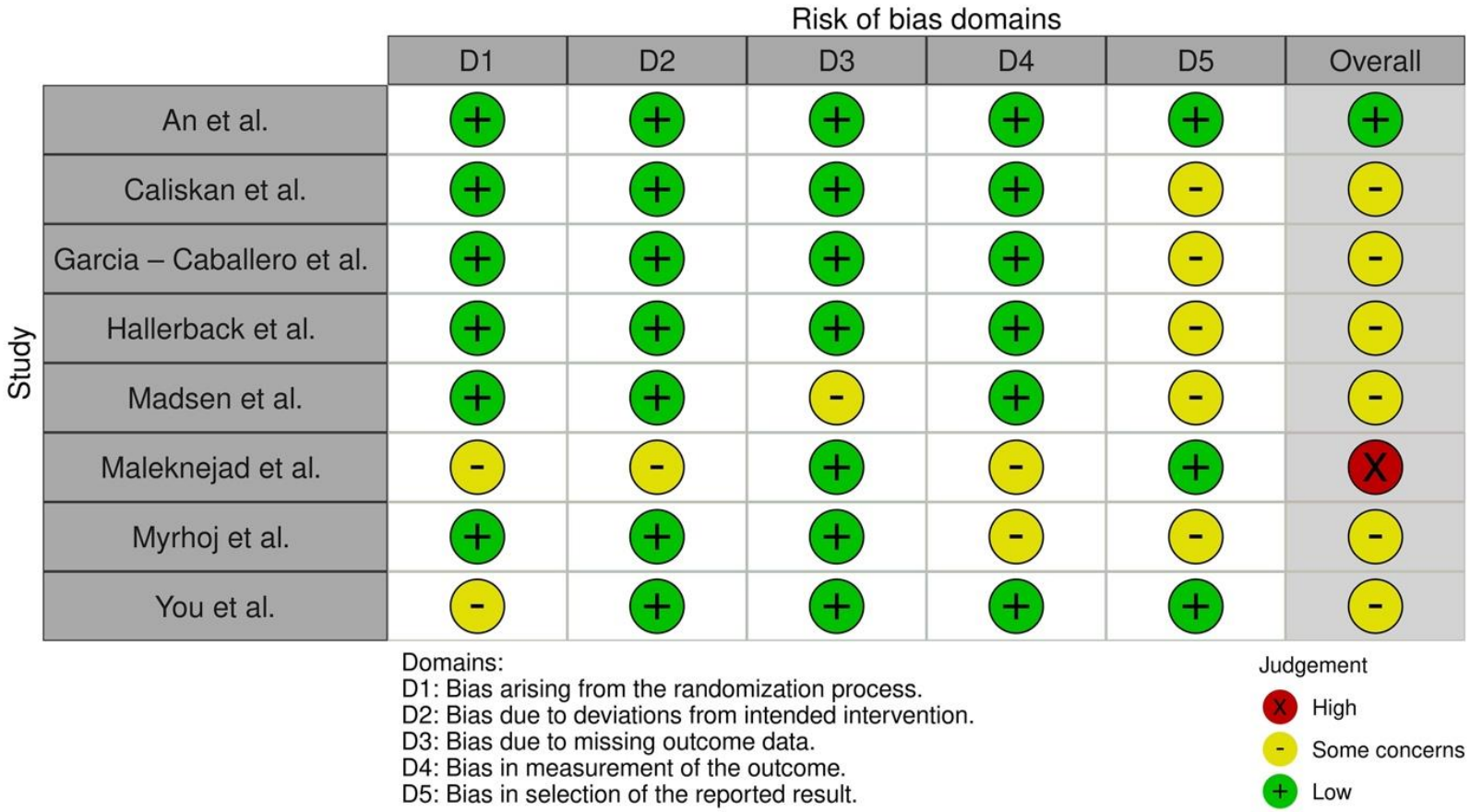

Figure 5. Traffic light plot.

3.4.4 GASTROINTESTINAL (GI) RECOVERY

Among the included studies, five reported time to flatus[196, 217, 247, 248, 258], six reported time to first stool[196, 217, 247, 248, 258, 259] and two studies reported the frequency of patients passing flatus or stool within 9 hours postoperatively or after commencing treatment.[256, 265] Notably, of all included studies none offered a strict clinical definition for POI.

Acetylcholinesterase inhibitors showcased enhanced gastrointestinal recovery in five studies compared to alternative treatment or placebo.[196, 247, 248, 258, 259] Of studies that compared against placebo[196, 247, 248, 259], Caliskan et al. found a 15-hour reduction in time to flatus and a 17-hour reduction in time to first stool in open abdominal aortic surgery ($p<0.05$).[196] Additionally, Hallerback et al. also demonstrated a reduction in time to first stool after open cholecystectomy with neostigmine and propranolol, with a reduction of 22 hours ($p<0.01$)[259] and You et al. reported significant reductions following open and laparoscopic gastrectomy for acupoint and IM neostigmine in both time to first flatus and time to first stool, with greatest results in the acupoint group ($p<0.01$).[247] Furthermore, Maleknjad et al. with NG pyridostigmine reported a significant reduction in time to the first flatus of 27.0 hours and time to the first stool of 31.3 hours with pyridostigmine ($p=0.001$).[248] Lastly, Garcia-Caballero et al. demonstrated a significant reduction in time to flatus of 21 hours and 40 hours to first stool following open cholecystectomy with a combination of intramesenteric bupivacaine, SC neostigmine and IV propranolol compared to open cholecystectomy without intervention ($p<0.01$).[258]

Three studies did not identify significant improvements in gastrointestinal recovery. Madsen et al. and Myrhoj et al. despite reported improved rates of passage of flatus or stool within 9 hours did reach statistical significance.[256, 265] Additionally, An et al. reported a significant reduction in time to flatus of 5.82 hours with sugammadex in comparison to

pyridostigmine in laparoscopic cholecystectomy (p=0.001) and a non-statistical significant reduction in time to stool.[217] A summary of the findings is provided in Table 5.

Table 5. Reported results for gastrointestinal recovery.

Reference	Intervention	Control	Time to flatus (h)					Time to stool (h)					Trial arm favoured
			Intervention	**n**	**Control/ comparison**	**n**	**p-value**	**Intervention**	**n**	**Control/ comparison**	**n**	**p-value**	
An et al.[217]	Pyridostigmine + glycopyrrolate	Sugammadex	20.85 (6.36-20.25)	53	15.03 (16.34-25.86)	49	0.001	47.26 (38.72-68.54)	53	38 (25.07-64.74)	49	0.087	Sugammadex
Caliskan et al.[196]	Neostigmine	Placebo	21 ± 15	18	36 ± 19	16	<0.05	58 ± 41	18	75 ± 48	16	<0.05	Neostigmine
Garcia – Caballero et al.[258]	Neostigmine + propranolol	Open cholecystectomy with no intervention	48 [45-72]	17	60 [24-90]	20	N.S	96 [45-125]	17	96 [60-125]	20	N.S	Neostigmine + propranolol + bupivacaine
	Neostigmine + propranolol + bupivacaine		39 [24-69]	19			<0.01	56 [24-69]	19			<0.01	
	Neostigmine + Bupivacaine		48 [24-96]	20			N.S	72 [36-120]	20			<0.001	
	Laparoscopic		10 [8-14]	20			<0.001	36 [24-40]	20			<0.05	
Hallerback et al.[259]	Neostigmine + propranolol	Placebo	-	-	-	-	-	68 ± 6	16	90 ± 7	17	<0.01	Neostigmine + propranolol
	Neostigmine		-	-	-	-	-	82 ± 6	18			N.S	
Malekneja d et al.[248]	Pyridostigmine	Placebo	5.4 ± 4.7	20	32.4 ± 9.9	20	0.001	4.9 ± 3.4	20	36.2 ± 10.3	20	0.001	Pyridostigmine
You et al.[247]	Acupoint	Standard therapy	2.3 ± 0.56	67	44.15 ± 1.69	53	<0.01	2.43 ± 0.61	67	50.02 ± 1.63	53	<0.01	Neostigmine
	Intramuscular		8.13 ± 1.38	63			<0.01	9.78 ± 1.66	67			<0.01	

	Acupuncture		40.34 ± 2.22	59			N.S	47.44 ± 1.56	59			N.S	
			Passing flatus or stool within 9 hours post-op					-	-	-	-	-	-
			Intervention	**n**	**Control/ Comparison**	**n**	**p-value**	-	-	-	-	-	-
Madsen et al.[265]	Neostigmine	Ceruletide	58% (36-78, 95% CI)	24	41% (22-63%, 95%CI)	24	N.S	-	-	-	-	-	-
Myrhoj et al.[256]	Neostigmine	Placebo	19% (9-34, 95% CI)	42	34% (20-50, 95%CI)	44	-	-	-	-	-	-	-

Data presented as mean (± SD); median (IQR); median [Range]
NS, Not statistically significant; 95% CI, 95 % confidence interval; -, Not available.

3.4.5 REPORTED SIDE EFFECTS

Four studies reported side effects in the intervention arms[196, 217, 247, 258] and two other studies mentioned no significant complications.[248, 256] An et al. reported a significantly higher percentage of patients with dry mouth following neostigmine against sugammadex administration (32 vs. 10.2%, p=0.008).[217] Caliskan et al. reported significantly lower levels of nausea for the intervention arm ($p<0.05$), and two patients suffered arrhythmias in the neostigmine group ($p>0.05$).[196] Garcia-Caballero et al. reported significantly lower frequency of patients with abdominal pain who were given neostigmine with and without bupivacaine (29-30%, no p-value provided) compared to the open cholecystectomy control group (45%, no p-value provided).[258] You et al. reported significant difference in the acupoint neostigmine against the IM neostigmine group, with reduced nausea (p=0.013), vomiting (p=0.027), diarrhea(p=0.042), epiphora (p=0.031), delirium (p=0.031), and anxiety (p=0.038).[247] The provided side effects are summarised in Table 6.

3.4.6 LENGTH OF HOSPITAL STAY

Only one study reported length of stay. Caliskan et al. demonstrated no difference in length of stay in the neostigmine or placebo arm (mean 5 days ± 2).[196]

Table 6. Reported secondary outcomes and side-effects.

	An et al.[217]			**Caliskan** et al.[196]			**Garcia – Caballero** et al.[258]				**You** et al.[247]		
	Pyridostigmine	**Sugammadex**	**p-value**	**Neostigmine**	**Placebo**	**p-value**	**OC + neostigmine + propranolol**	**OC + neostigmine + propranolol + bupivacaine**	**OC**	**p-value**	**Acupoint**	**IM**	**p-value**
Nausea	15.1%	16.3%	N.S	16.7%	56.3%	<0.05	-	-	-	-	4.5%	17.9	0.013
Vomiting	5.7%	8.2%	N.S	0%	12.5%	N.S	-	-	-	-	3%	13.4%	0.027
Dry Mouth	32%	10.2%	0.008	-	-	-	-	-	-	-	-	-	-
Renal failure	-	-	-	11.1%	0%	N.S	-	-	-	-	-	-	-
Resp failure	-	-	-	11.1%	6.25%	N.S	-	-	-	-	-	-	-
Arrhythmia	-	-	-	11.1%	0%	N.S	-	-	-	-	-	-	-
Abdominal discomfort 1st day	-	-	-	-	-	-	30%	29%	45%	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	40.3%	56.72 %	0.042
Epiphora	-	-	-	-	-	-	-	-	-	-	1.5%	10.45 %	0.031
Delirium	-	-	-	-	-	-	-	-	-	-	1.5%	10.45 %	0.031
Anxiety	-	-	-	-	-	-	-	-	-	-	4.5%	14.9%	0.038
Length of stay (days)	-	-	-	5 ± 2	5 ± 2	N.S	-	-	-	-	-	-	-

Data presented as mean (± SD) or frequency (%)
OC, Open Cholecystectomy; NS, Not statistically significant; -, Not available.

3.5 DISCUSSION

In this systematic review of eight RCTs of acetylcholinesterase inhibitors to reduce gastrointestinal function recovery time following abdominal surgery, five studies showed a significant reduction in time to return of gastrointestinal function, with improvements in time to first stool ranging from 17-47.59 hours albeit using widely variable route of administration and timing.[196, 247, 248, 258, 259]

In this review, acetylcholinesterase inhibitors were shown to improve gastrointestinal motility following abdominal surgery; however, the conclusions are limited due to the large variations in dosing, route of administration, type of surgery and overall results leading to low quality of evidence for their use. An issue highlighted by this review is that the included studies report the time to gastrointestinal recovery and do not report the incidence of POI or use a validated gastrointestinal recovery measure such as GI-2.[25] Furthermore, the included studies are outdated, ranging over many decades (1986 to 2019), with only two being published in the last 13 years, and most studies investigating open surgical approaches not based in a modern ERP setting.[217, 247] Overall, this meant a meta-analysis of data would be unreliable and of little clinical value.

This systematic review builds upon our clinical scoping review [266], which revealed the utilisation of acetylcholinesterase inhibitors in surgery. These inhibitors were shown to reverse neuromuscular blockade, treat ACPO, and potentially improve gastrointestinal recovery postoperatively. This emphasised the need for a more comprehensive examination of the most robust evidence, namely RCTs, before we could consider the routine use of acetylcholinesterase inhibitors to improve gastrointestinal recovery postoperatively. As no previous systematic review has investigated this topic and only a limited number of papers were identified on preliminary screening, we opted to include all

abdominal surgical cases at risk POI. This inclusion meant we included cases with bowel resection[247, 248, 256] along with procedures not involving the gastrointestinal tract[196, 217, 258, 259, 265], albeit with an acknowledgement of this limitation.

Acetylcholinesterase inhibitors impact the return of gastrointestinal function through two possible mechanisms. The first is by increasing acetylcholine availability at the neuromuscular junction causing activation of the myenteric plexus, resulting in direct gastrointestinal mass movement. Through this mechanism, neostigmine is used to treat ACPO.[197] Despite ACPO and POI representing two separate pathologies, the definitions are often mixed, resulting in papers grouping patients with ACPO and POI.[257] ACPO results from severe medical or surgical illness, characterised by distention of the colon and uncoordinated bowel motility.[252] POI, on the other hand, results from surgical stimuli, leading to mainly small bowel dilatation via various mechanisms.[19] Regardless, gastrointestinal mass movement secondary to acetylcholinesterase inhibitors represents the resolution of the gastrointestinal discoordination or paralysis, which is a crucial feature of both pathologies.

The second method by which acetylcholinesterase inhibitors may influence development of POI, and facilitate the return of gastrointestinal function, is via modulation of the CAIP. This is a key pathway in the secondary inflammatory phase of POI, starting from around 3 hours postoperatively.[45, 63, 149, 252] During this time, the CAIP has the potential to be modulated by acetylcholinesterase inhibitors. In the included studies of this systematic review, only three were timed to commence their interventional treatment before the potential establishment of the CAIP mechanism and continued until the recovery of bowel function.[247, 258, 259] Given the potential to modulate the CAIP and direct gastrointestinal stimulation, there is scope for a trial using acetylcholinesterase inhibitors to prevent POI.

Pyridostigmine provides a potential option to improve the return of gastrointestinal function and prevent prolonged POI as part of an ERP. It can be given orally and early with a preference over neostigmine which is administered intravenously and requires cardiac monitoring due to concerns of cardiac arrhythmia. An et al. in their use of pyridostigmine in reversal of neuromuscular blockade, demonstrated that sugammadex resulted in an earlier return of flatus but no difference in return of stool.[217] This is likely a result of co-administration of glycopyrrolate with pyridostigmine to counteract its cholinergic side effects. Given pyridostigmine is not used commonly in reversal of neuromuscular blockade due to its prolonged onset of action, the evidence for pyridostigmine in this setting is of little benefit. Maleknejad et al. in their single-blind RCT, demonstrated a reduction in time to first stool using pyridostigmine to treat established POI.[248] However, this study had a high risk of bias and did not use pyridostigmine to modulate the development of POI via the CAIP and improve return of gastrointestinal function. This study also used mainly obstetric patients and excluded colorectal patients, who carry the greatest risk of POI.

Acetylcholinesterase inhibitors have well-known cholinergic side-effects, including abdominal pain, hypersalivation and vomiting. In particular, neostigmine can cause bradycardia, heart block and life-threatening arrhythmias.[197] Due to the cholinergic effects, acetylcholinesterase inhibitor use is contraindicated in patients with a risk of arrhythmia due to cardiac disease, as well as asthma and neurological disorders such as Parkinson's disease and epilepsy.[270] In our review there was a significant increase in patients with dry mouth following neostigmine against sugammadex administration (32 vs. 10.2%, p=0.008).[217] As well, only one study reported arrhythmias associated with neostigmine use; however, this did not reach statistical significance.[196] In our own experience, we have performed a 15-patient pilot study looking at pyridostigmine to improve return of

gastrointestinal function following colorectal surgery.[249] This study demonstrated no significant side effects and a median time to return of gastrointestinal function of 2 days (1-4).

In addition to the limitations mentioned above, we noted a significant lack of data in patients undergoing colorectal resection, despite these patients having the greatest risk of POI in abdominal surgery.[17] The included studies have low samples sizes, significant concerns of bias, and lack of follow-up and adverse events data, which reduces the overall quality of the studies. Therefore, the benefits of administering acetylcholinesterase inhibitors to improve the return of gastrointestinal function remain inconclusive.

Currently, we are conducting a double blinded RCT investigating pyridostigmine as part of an ERP to improve the return of gastrointestinal function and prevent POI (registered at https://www.anzctr.org.au/ - ACTRN12621000530820). This study addresses the gaps identified in this review, focusing on POI in high-risk colorectal surgery patients. Pyridostigmine, chosen for its convenience as an oral tablet and no need for cardiac monitoring, is being evaluated with the validated gastrointestinal outcome measure (GI-2).[25] This study includes 130 patients, with statistical power for the primary outcome measure. Additionally, in contrast to prior studies, our RCT defines POI as participants not achieving GI-2 by day four. Notably, our research also places a particular focus on patient-reported side effects and complications, an aspect that was often inadequately reported in the included studies in this review.

3.6 CONCLUSION

This systematic review highlights that there is limited supportive evidence for using acetylcholinesterase inhibitors to improve the return of gastrointestinal function or prevent

POI; however, studies are heterogenous and of low-grade quality. To answer if acetylcholinesterase inhibitors can reduce the time to return of gastrointestinal function, high-quality double blinded randomised controlled trials are required.

CHAPTER 4: EFFECT OF NEUROMUSCULAR REVERSAL WITH NEOSTIGMINE/GLYCOPYRROLATE VERSUS SUGAMMADEX ON POSTOPERATIVE ILEUS FOLLOWING COLORECTAL SURGERY

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Tech Coloproctol. 2022 Sep 5. https://doi.org/10.1007/s10151-022-02695-w

Statement of Authorship

Title of Paper	Effect of neuromuscular reversal with neostigmine/glycopyrrolate versus sugammadex on postoperative ileus following colorectal surgery.
Publication Status	Published
Publication Details	Traeger L, Hall TD, Bedrikovetski S, Kroon HM, Dudi-Venkata NN, Moore JW, Sammour T. Effect of neuromuscular reversal with neostigmine/glycopyrrolate versus sugammadex on postoperative ileus following colorectal surgery. Tech Coloproctol. 2023 Mar;27(3):217-226. https://doi.org/10.1007/s10151-022-02695-w.

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Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Before examining the impact of ACIs to improve GI recovery after colorectal surgery, I review our local experience regarding the choice of neuromuscular reversal agents (neostigmine/glycopyrrolate or sugammadex) and the influence on the return of GI function. This is the first study to explore this correlation, employing a validated outcome measure to assess GI recovery.

4.1 ABSTRACT

Background: Postoperative ileus (POI) is a common complication following colorectal surgery and is mediated in part by the cholinergic anti-inflammatory pathway (CAIP). Neostigmine (acetylcholinesterase inhibitor), co-administered with glycopyrrolate, is frequently given for neuromuscular reversal before tracheal extubation and modulates the CAIP. An alternative reversal agent, sugammadex (selective rocuronium or vecuronium binder), acts independently from the CAIP. The aim of our study was to assess the impact of neuromuscular reversal agents used during anaesthesia on gastrointestinal recovery.

Methods: Three hundred thirty-five patients undergoing elective colorectal surgery at the Royal Adelaide Hospital between January 2019 and December 2021 were retrospectively included. The primary outcome was GI-2, a validated composite measure of time to diet tolerance and passage of stool. Demographics, 30-day complications and length of stay were collected. Univariate and multivariate analyses were performed.

Results: Two hundred twenty-four (66.9%) patients (129(57.6%) males and 95(42.4%) females, median age 64(19-90) years) received neostigmine/glycopyrrolate and 111 (33.1%) received sugammadex (62(55.9%) males and 49(44.1%) females, median age 67(18-94) years). Sugammadex patients achieved GI-2 sooner after surgery (median 3(0-10) vs. 3(0-12) days, p=0.036), and reduced time to first stool (median 2(0-10) vs. 3(0-12) days, p=0.035). Rates of POI, complications and length of stay were similar. On univariate analysis, POI was associated with smoking history, previous abdominal surgery, colostomy formation, increased opioid use and postoperative hypokalaemia ($p<0.05$). POI was associated with increased complications, including anastomotic leak and prolonged hospital stay ($p<0.001$). On multivariate analysis neostigmine, bowel anastomoses and increased postoperative opioid use ($p<0.05$) remained predictive of time to GI-2.

Conclusions: Patients who received sugammadex had a reduced time to achieving first stool and GI-2. Neostigmine use, bowel anastomoses and postoperative opioid use were associated with delayed time to achieving GI-2.

4.2 INTRODUCTION

Postoperative ileus (POI) is a common complication following major abdominal surgery, particularly colorectal surgery, occurring in up to 25% of patients resulting in significant morbidity and mortality.[45] POI occurs in two phases: an initial neurogenic phase followed by a secondary inflammatory phase.[45] The inflammatory phase starts approximately three hours postoperatively, releasing inflammatory mediators that affect bowel function for a variable length of time.[24, 45] This inflammatory cascade is mediated, in part, by the cholinergic anti-inflammatory pathway (CAIP).[149, 262]

To facilitate abdominal surgery, most patients are paralysed with a non-depolarising neuromuscular blocking drug (NMBD) on induction. These agents competitively antagonise acetylcholine at postsynaptic nicotinic receptors in the neuromuscular junction (NMJ).[213] Upon completion of surgery, any residual paralysis is reversed before tracheal extubation of the patient with either acetylcholinesterase inhibitors, most commonly neostigmine, or an encapsulating agent named sugammadex. Acetylcholinesterase inhibitors competitively bond with acetylcholinesterase in the synaptic cleft of the NMJ, reducing the hydrolysis of acetylcholine.[215] The increased concentration of acetylcholine competitively reverses the action of the NMBD at the NMJ.[192] The increase in acetylcholine, however, is not limited to the NMJ.[222] Peripheral muscarinic receptors also use acetylcholine and, if left unopposed, produce muscarinic side effects thus require co-administration of an anticholinergic agent (such as glycopyrrolate). The effect of neostigmine and glycopyrrolate as neuromuscular reversal agents on the CAIP and their overall impact on bowel motility following surgery remains unclear.[266]

Sugammadex is a modified γ-cyclodextrin that encapsulates the aminosteroid NMBDs, rocuronium and vecuronium, with high affinity.[221] Sugammadex is a large molecule that

does not readily enter the NMJ; acting mainly within the circulating plasma. Free NMBD molecules in the plasma are rapidly chelated, creating a concentration gradient promoting the movement of NMBD from the NMJ into the plasma where they are once again sequestered.[222] The reduction in NMBD available at the NMJ, results in the reversal of the neuromuscular blockade. Sugammadex acts independently of cholinergic transmission and therefore does not require coadministration of anticholinergic agents, and thus has no potential to act on the CAIP.[223] Sugammadex is however speculated to alter gut motility and gastric emptying due to its affinity to bind with steroid hormones.[216, 217]

As sugammadex and neostigmine could influence the return of bowel function, several studies have investigated their impact with varied results.[216-220] However, these studies do not compare neostigmine and sugammadex using a validated gastrointestinal recovery outcome measure, such as GI-2.[25] Our aim was to identify the effect of neostigmine/glycopyrrolate or sugammadex on gastrointestinal recovery following colorectal surgery using GI-2.

4.3 MATERIALS AND METHODS

This study is reported using the Strengthening The Reporting of Observational studies in Epidemiology (STROBE) guidelines (Appendix B)[271], and was approved by the Central Adelaide Local Health Network Human Research Ethics Committee. A waiver of consent for retrospective patients was provided in accordance with the guidelines provided by the National Health and Medical Research Council's (NHMRC).[272]

4.3.1 PATIENT SELECTION

This study was performed at the Colorectal Unit of the Royal Adelaide Hospital (RAH), a tertiary referral centre in South Australia, Australia. Patients were identified from the

elective admission lists and underwent surgery between January 2019 to December 2021. All patients at the RAH, are placed on an enhanced recovery pathway (ERP). The ERP protocol can be found at www.tinyurl.com/raheras.

4.3.2 INCLUSION AND EXCLUSION CRITERIA

Consecutive elective colorectal patients over 18 years old who underwent major bowel surgery, consisting of large or small bowel resection, reversal or stoma formation, were included. Pelvic exenterations were excluded due to the associated high morbidity and variables affecting return of bowel function. Robotic cases were excluded as they are performed at another geographic site and transferred to the study hospital for postoperative care. Patients who did not receive a neuromuscular reversal agent, received both agents, non-operative admissions, or prescribed acetylcholinesterase inhibitors as part of the 'Pyridostigmine to reduce the incidence of postoperative ileus following colorectal surgery (PyRICo – P)' study were excluded.[249]

4.3.3 DATA COLLECTION

Data were collected retrospectively from paper and electronic medical records by two authors (LT and TH). Anaesthetist choice of neostigmine/glycopyrrolate or sugammadex was collected. Known risk factors for the development of POI were collected.[27, 84, 100] Baseline demographics such as age, body mass index (BMI), smoking history, congestive cardiac failure (CCF), chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus, regular steroid use, ascites or previous abdominal surgery history were recorded, along with preoperative haemoglobin, total protein and albumin. Operative data included the diagnosis (benign/malignant), surgical approach (open/laparoscopic), laparoscopic to open conversion, procedure type, stoma formation and duration of surgery, and intraoperative and postoperative fluid administration. Postoperative data included

opioid requirements in morphine equivalents (intraoperative, postoperative recovery and day one to four use) calculated using Opioid Calculator v2.9.1 (Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists, Australia),

4.3.4 OUTCOMES

The primary outcome was gastrointestinal recovery measured retrospectively using GI-2: a validated outcome measure comprised of time to first stool and tolerance of solid diet without significant nausea or vomiting.[25] Secondary outcomes included POI, defined as not achieving GI-2 by day 4 postoperatively, as well as time to first stool, time to tolerance of oral diet, and nasogastric tube (NGT) reinsertion incidence for both groups. Furthermore, postoperative outcomes including intensive care admission and length of stay were recorded. Thirty-day complications, Clavien-Dindo (CD) grades, return to theatre, and readmission rates were collected.[273] Anastomotic leak was defined by patients having extra-luminal presence of contrast fluid on a contrast-enhanced computed tomography scan and/or evidence of leakage of luminal contents from a surgical join on reintervention within 30 days.[274]

4.3.5 STATISTICAL ANALYSIS

A priori power calculation was performed using G*Power 3.1 (Franz Faul, Universitat Kiel, Germany), with the best available data from Hunt et al. showing a mean return of stool with sugammadex of 1.7d (SD 1.2) and 2.2d (SD 1.3) (converted from hours) with neostigmine, as no previous studies used GI-2.[220] Using an α error of 0.05, ß error of 0.2, power of 0.8 and an effect size of 0.40, a minimum sample size of 100 patients in each arm was required. Numerical data are presented as median (IQR [range]) or mean (standard deviation) depending on parametricity identified with the Shapiro-Wilk test. Univariate analysis was performed using the Mann-Whitney U for nonparametric variables

or student-t test for normally distributed continuous variables. The χ^2 or Fisher's exact test (when expected n<5) for categorical variables. All collected variables were used in the univariate linear regression analysis on log-normal transformed time to GI-2. Statistically significant variables were then used for multivariate linear regression analyses, to determine predictors of GI-2. Data for multivariate linear regression analyses were evaluated and met all linear assumptions. P-values of <0.05 were considered statistically significant. A one-day reduction in GI-2 was considered clinically significant. Statistical analysis was performed using SPSS 28.0 (SPSS Inc., Armonk, NY, USA).

4.4 RESULTS

Of 1,115 elective colorectal admissions during the study period, 335 patients were included (Figure 6).

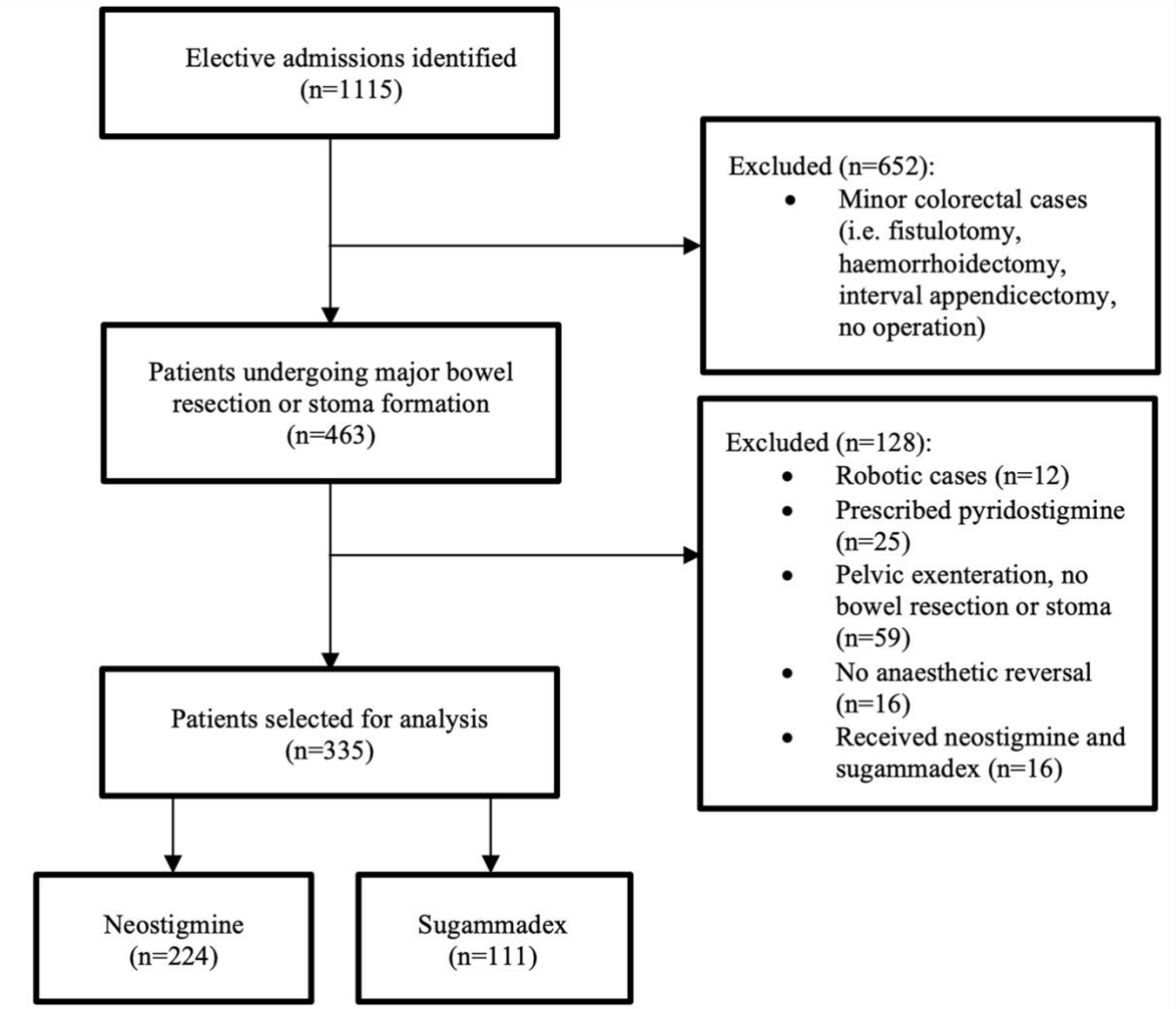

Figure 6. Flowchart of patient selection

224 (66.9%) patients received neostigmine and glycopyrrolate (129 (57.6%) males and 95 (42.4%) females, median age 64 (19-90) years), and 111 (33.1%) received sugammadex (62 (55.9%) males and 49 (44.1%) females, median age 67 (18-94) years). Three patients in the neostigmine group were also given atropine, and 7 patients in the sugammadex received glycopyrrolate to treat intraoperative bradycardia. Both groups' baseline patient and operative characteristics are summarised in Table 7. Patients receiving sugammadex had a higher ASA class $\geq$3 (60.4% vs. 45.1%, p<0.001), a greater BMI (median 28.7 vs. 26.8 kg/m^2, p=0.003), were more comorbid with COPD (15.3% vs. 6.7%, p=0.012) and hypertension (56.8% vs. 41.5%, p=0.008) and were more likely to undergo laparoscopic surgery (66.7% vs. 50.9%, p=0.006).

Table 7. Comparison of baseline patient and operative characteristics between neuromuscular reversal agents.

	Neostigmine (n= 224)	Sugammadex (n= 111)	p-value
Baseline characteristics			
Age; years	64 (53-72 [19-90])	67 (57-76 [18-94])	0.056
Sex			0.763
Female	95 (42.4%)	49 (44.1%)	
Male	129 (57.6%)	62 (55.9%)	
BMI; kg/m^2	26.8 (23.4-30.4 [15.9 -58.8])	28.7 (24.7-32.9 [18.2 – 73.0])	**0.003**
ASA			**<0.001**
I	5 (2.2%)	3 (2.7%)	
II	118 (52.7%)	41 (36.9%)	
III	101 (45.1%)	62 (55.9%)	
IV	0 (0.0%)	5 (4.5%)	
Smoking history			0.601
Active	46 (20.5%)	19 (17.1%)	
Ex-smoker	66 (29.5%)	38 (34.2%)	
CCF	7 (3.1%)	4 (3.6%)	0.757
COPD	15 (6.7%)	17 (15.3%)	**0.012**
Hypertension	93 (41.5%)	63 (56.8%)	**0.008**
Diabetes mellitus			0.074
Prescribed tablets	37 (16.5%)	21 (18.9%)	
Prescribed insulin	2 (0.9%)	5 (4.5%)	
Prescribed regular steroids	9 (4.0%)	10 (9.0%)	0.063
Ascites	2 (0.9%)	4 (3.6%)	0.096
Previous abdominal surgery	135 (60.3%)	59 (53.2%)	0.214
Preoperative haemoglobin; g/L	136 (122-147 [81-177])	134 (121-144 [81-174])	0.221
Preoperative total protein; g/L	73 (70-77 [53-93])	73 (68-78 [56-95])	0.575
Missing	*2*	*2*	
Preoperative albumin; g/L	36 (34-40 [20-49])	36 (34-39 [22-46])	0.450
Missing	*1*	*1*	
Intraoperative characteristics			
Malignant diagnosis	123 (54.9%)	73 (65.8%)	0.058
Operations			0.888
Right sided †	70 (31.3%)	37 (33.3%)	
Left sided ‡	85 (37.9%)	43 (38.7%)	
Total colectomy, pan-proctocolectomy, completion colectomy	16 (7.1%)	10 (9.0%)	
Formation of stoma	8 (3.6%)	3 (2.7%)	
Small bowel resection or ileostomy reversal	45 (20.1%)	18 (16.2%)	
Surgical approach			**0.006**
Open	110 (49.1%)	37 (33.3%)	
Laparoscopic	114 (50.9%)	74 (66.7%)	
Conversion from laparoscopic to open §	19 (16.7%)	16 (21.6%)	0.369
Stoma formed	50 (22.3%)	22 (19.8%)	0.600
Stoma type			0.339
Ileostomy	33 (66.0%)	17 (77.3%)	
Colostomy	17 (34.0%)	5 (22.7%)	
Theatre duration; min	157 (110-194 [42-378])	170 (120-215 [29-433])	0.142
Postoperative characteristics			
Lowest postoperative potassium within POD 1-4, mmol/L	3.8 (3.5-4.0 [2.6-4.8])	3.8 (3.5-4.0 [2.7-5.1])	0.760
Missing	*2*	*0*	
Charted aperients	132 (58.9%)	67 (60.4%)	0.802

Intraoperative and recovery opioid use; MEQ	120 (88-163 [20-483])	129 (89-183 [25-768])	0.122
Total opioid use POD 1-4; MEQ	130 (52-227 [0-1831])	135 (57-295 [0-1385])	0.593
Total intraoperative fluids; ml	2000 (1000-2000 [158-5000])	2000 (1000-2000 [100-5000])	0.220
Total recovery fluids; ml	900 (500-1325 [0-3000])	1050 (500-1275 [0-4000])	0.478

Values are median (IQR [range]), mean (SD) or number (percentage).
†Includes ileocolic resection, extended/right hemicolectomy, transverse colectomy, subtotal colectomy;
‡Includes left hemicolectomy, sigmoidectomy, anterior resection, abdomino-perineal resection, reversal of Hartmann's procedure; §n=114 neostigmine, n=74 sugammadex.

Postoperatively, patients receiving sugammadex had a statistically significantly shortened median time to GI-2 (3(0-10) vs. 3(0-12) days, p=0.036) and a reduced median time to first stool (2(0-10) vs. 3(0-12), p=0.035). There were no significant differences in time to POI rates, NGT reinsertion, length of stay and 30-day complications between groups (Table 8).

Table 8. Postoperative outcomes comparing neuromuscular reversal agents.

	Neostigmine (n= 224)	Sugammadex (n= 111)	p-value
Gastrointestinal recovery			
GI-2; d	3 (2-5 [0-12])	3 (2-4 [0-10])	**0.036**
Time to first stool; d	3 (2-4 [0-12])	2 (1-4 [0-10])	**0.035**
Time to tolerance of oral diet; d	2 (1-4 [0-11])	2 (1-4 [0-10])	0.117
POI	65 (29.0%)	28 (25.2%)	0.466
NGT reinsertion	60 (26.8%)	29 (26.1%)	0.898
Complications and clinical outcomes			
ICU admission	11 (4.9%)	3 (2.7%)	0.402
Anastomotic leak†	13 (6.7%)	3 (3.0%)	0.279
CD grade			0.830
No complication	97 (43.3%)	43 (38.7%)	
1	22 (9.8%)	11 (9.9%)	
2	86 (38.4%)	50 (45.0%)	
3	8 (3.6%)	3 (2.7%)	
4	11 (4.9%)	4 (3.6%)	
Blood products transfusion required	9 (4.0%)	4 (3.6%)	>0.999
Return to theatre within 30 days	10 (4.5%)	4 (3.6%)	>0.999
Readmission within 30 days	28 (12.5%)	13 (11.7%)	0.836
Length of stay; days	5 (4-8 [1-60])	6 (4-8 [2-24])	0.844

Values are median (IQR [range]), mean (SD) or number (proportion).
† n=195 for neostigmine, n=99 for sugammadex.

Overall, 93 patients (27.8%) had a POI (Table 9). POI was more likely to occur in patients with a history of smoking (62.3% vs. 45.9%, p=0.025), previous abdominal surgery (68.8% vs. 53.7%, p=0.012), those who underwent open surgery (55.9% vs. 39.3%, p=0.006), and patients who had a colostomy formed (60.0% vs. 22.8%, p=0.005). Patients within postoperative day 1-4 with lower potassium (median 3.7 vs. 3.8 mmol/L, p=0.017), charted aperients (69.9% vs. 55.4%, p=0.015) and receiving more postoperative opioids (median 218 vs. 110 MEQ, p<0.001) developed POI. POI was associated with significantly more ICU admissions (9.7% vs. 2.1%, p=0.002), anastomotic leaks (13.9% vs. 2.3%, p<0.001), greater incidence of return to theatre (8.6% vs. 2.5%, p=0.012) and a higher CD grade of complications (p<0.001). Patients diagnosed with a POI had a 3-day increase in median length of stay (8(3-33) vs. 5(1-60) days, p<0.001).

Table 9. Univariate analysis for postoperative ileus of baseline, intra- and postoperative characteristics, and outcomes.

	Non-POI (n= 242)	POI (n= 93)	p-value
Baseline characteristics			
Age; years	64 (53-73 [18-94])	65 (58-75 [25-89])	0.233
Gender			0.141
Female	110 (45.5%)	34 (36.6%)	
Male	132 (54.5%)	59 (63.4%)	
BMI; kg/m^2	27.1 (23.8-31.2 [15.9-58.8])	27.3 (24.4-31.6 [15.9 – 73.0])	0.378
ASA class			0.108
I	8 (3.3%)	0 (0.0%)	
II	120 (49.6%)	39 (41.9%)	
III	110 (45.5%)	53 (57.0%)	
IV	4 (1.7%)	1 (1.1%)	
Smoking history			**0.025**
Active	42 (17.4%)	23 (24.7%)	
Ex-smoker	69 (28.5%)	35 (37.6%)	
CCF	8 (3.3%)	3 (3.2%)	>0.999
COPD	21 (8.7%)	11 (11.8%)	0.380
Hypertension	111 (45.9%)	45 (48.4%)	0.679
Diabetes mellitus			0.744
Prescribed tablets	43 (17.8%)	15 (16.1%)	
Prescribed insulin	6 (2.5%)	1 (1.1%)	
Prescribed regular steroids	16 (6.6%)	3 (3.2%)	0.298
Ascites	5 (2.1%)	1 (1.1%)	>0.999
Previous abdominal surgery	130 (53.7%)	64 (68.8%)	**0.012**
Preoperative haemoglobin; g/L	135 (122-147 [81-177])	134 (122-147 [81-168])	0.786
Preoperative total protein; g/L	73 (69-78 [53-95])	73 (70-76 [58-93])	0.640
Missing	*3*	*1*	
Preoperative albumin; g/L	36 (34-40 [22-49])	36 (34-39 [20-49])	0.575
Missing	*1*	*1*	
Intraoperative characteristics			
Malignancy diagnosed	146 (60.3%)	50 (53.8%)	0.275
Operation			0.228
Right sided †	74 (30.6%)	33 (35.5%)	
Left sided ‡	88 (36.4%)	40 (43.0%)	
Total colectomy, pan-proctocolectomy, completion colectomy	23 (9.5%)	3 (3.2%)	
Formation of stoma	9 (3.7%)	2 (2.2%)	
Small bowel resection or ileostomy reversal	48 (19.8%)	15 (16.1%)	
Surgical approach			**0.006**
Open	95 (39.3%)	52 (55.9%)	
Laparoscopic	147 (60.7%)	41 (44.1%)	
Conversion from laparoscopic to open	25 (17.1%)	10 (24.4%)	0.292
Stoma formed	57 (23.6%)	15 (16.1%)	0.138
Stoma type			**0.005**
Ileostomy	44 (77.3%)	6 (40.0%)	
Colostomy	13 (22.8%)	9 (60.0%)	
Theatre duration; minutes	160 (115-202 [29-433])	161 (118-195 [48-352])	0.969
Postoperative characteristics			
Lowest postoperative potassium within POD 1-4; mmol/L	3.8 (3.6-4.0 [2.6-5.1])	3.7 (3.4-4.0 [2.9-4.6])	**0.017**
Missing	*1*	*1*	
Charted aperients	134 (55.4%)	65 (69.9%)	**0.015**

Intraoperative and recovery opioid use; MEQ	124 (90-174 [20-768])	120 (80-163 [20-445])	0.571
Total opioid use POD 1-4; MEQ	110 (42-203 [0-1385])	218 (113-439 [10-1831])	**<0.001**
Total intraoperative fluids; ml	2000 (1000-2000 [100-5000])	2000 (1000-2000 [158-3000])	0.085
Total recovery fluids; ml	1000 (500-1300 [0-4000])	1000 (500-1400 [0-2500])	0.627
Outcomes			
ICU admission	5 (2.1%)	9 (9.7%)	**0.002**
Anastomotic leak [§]	5 (2.3%)	11 (13.9%)	**<0.001**
Highest CD grade			**<0.001**
No complication	140 (57.9%)	0 (0.0%)	
1	33 (13.6%)	0 (0.0%)	
2	59 (24.4%)	77 (82.8%)	
3	5 (2.1%)	6 (6.5%)	
4	5 (2.1%)	10 (10.8%)	
Highest CD grade (excluding POI)			**<0.001**
No complication	149 (61.6%)	33 (35.5%)	
1	40 (16.5%)	18 (19.4%)	
2	43 (17.8%)	26 (28.0%)	
3	5 (2.1%)	6 (6.5%)	
4	5 (2.1%)	10 (10.8%)	
Blood products transfusion required	8 (3.3%)	5 (5.4%)	0.380
Return to theatre within 30 days	6 (2.5%)	8 (8.6%)	**0.012**
Readmission within 30 days	29 (12.0%)	12 (12.9%)	0.818
Length of stay; days	5 (3-6 [1-60])	8 (6-10 [3-33])	**<0.001**

Values are median (IQR [range]), mean (SD) or number (proportion).
[†] Includes ileocolic resection, extended/right hemicolectomy, transverse colectomy, subtotal colectomy; [‡] Includes left hemicolectomy, sigmoidectomy, anterior resection, abdominoperineal resection, reversal of Hartmann's procedure; [§] n=217 for no-POI, n=79 for POI.

On univariate and multivariate linear regression analyses, neostigmine/glycopyrrolate use ($p=0.034$), anastomosis formation ($p<0.001$) and increased postoperative opioid use were predictive of time to achieving GI-2 ($p<0.001$) (Table 10).

Table 10. Univariate and multivariate linear regression analyses of variables predictive of GI-2.

	Univariate			Multivariate		
	ß	**95% CI**	**p-value**	**ß**	**95% CI**	**p-value**
Neostigmine/ Glycopyrrolate use	0.067	(0.008, 0.126)	**0.026**	0.060	(0.004, 0.116)	**0.034**
Smoking history	0.058	(0.003, 0.114)	**0.041**	0.036	(-0.016, 0.088)	0.175
Previous abdominal surgery	0.057	(0.001, 0.114)	**0.047**	0.018	(-0.039, 0.075)	0.543
Open surgical approach	0.081	(0.025, 0.137)	**0.005**	0.049	(-0.008, 0.107)	0.093
Anastomosis formed	0.103	(0.035, 0.170)	**0.003**	0.117	(0.052, 0.181)	**<0.001**
Postoperative serum potassium level	0.098	(0.031, 0.166)	**0.005**	0.064	(0.000, 0.128)	0.051
Charted aperients	0.059	(0.003, 0.116)	**0.041**	0.053	(0.000, 0.106)	0.051
Postoperative opioids use	0.129	(0.075, 0.184)	**<0.001**	0.125	(0.072, 0.179)	**<0.001**
Anastomotic leak	0.215	(0.086, 0.344)	**0.001**	0.082	(-0.090, 0.254)	0.350
Intensive care unit admission	0.204	(0.065, 0.342)	**0.004**	0.087	(-0.053, 0.228)	0.224
Return to theatre	0.187	(0.048, 0.325)	**0.008**	0.052	(-0.131, 0.234)	0.578

4.5 DISCUSSION

This study demonstrates a statistically but not clinically relevant difference in time to GI-2 achievement favouring sugammadex used in neuromuscular reversal compared to neostigmine. We also found a clinically significant one-day reduction in time to first stool favouring sugammadex use. However, the choice of neuromuscular reversal agent did not impact the incidence of POI as defined by GI-2.

These results support previous studies that have demonstrated a reduced time to return of gastrointestinal function with sugammadex. In abdominal surgery studies, sugammadex resulted in an earlier return of flatus when investigating laparoscopic cholecystectomy, but no change in time to first stool.[217] The most extensive study to date included over 8000 patients undergoing abdominal surgery without differentiating types of surgery. It investigated the impact of reversal agents on gastrointestinal recovery, showing that sugammadex resulted in a faster first bowel movement than neostigmine.[218] Several studies have also investigated colorectal surgical patients, favouring sugammadex.[219, 220] In our cohort, although sugammadex patients had an earlier time to first stool, there was no reduction in the risk of developing POI and no clinical difference in time taken for gastrointestinal recovery as defined by GI-2.

Neostigmine did not have a beneficial effect on the return of GI function post-operatively, and there are several plausible explanations for this. The overall duration of action for neostigmine is 20-30 minutes.[188] Given that the CAIP develops from approximately 3 hours postoperatively, this could explain why there is little impact on POI rates. In addition, while historical evidence suggested that co-administration with glycopyrrolate would not reverse the promotility effect of neostigmine [275], contemporary studies have suggested this does lead to a delay in return of gastrointestinal recovery following intraperitoneal

surgery.[218] The delay in the return of gastrointestinal function likely results from neostigmine's cholinergic effects being negated due to its co-administration of the anticholinergic glycopyrrolate. This is supported by the pharmacology of glycopyrrolate, with the duration of action being three to five times longer than neostigmine.[276] This accounts for the observed outcomes of the current study compared to sugammadex, a selective agent without anticholinergic activity.[277]

In our study, the reversal agent was chosen by anaesthetist preference, without surgical input. Patients receiving sugammadex were more overweight and comorbid. Compared to neostigmine, sugammadex demonstrates a faster onset of reversal, the potential to reverse deeper neuromuscular blockade, decreased postoperative nausea and vomiting, shortened recovery time, and minimal side effects.[278] Hence, sugammadex was chosen to reverse these higher risk patients to minimise postoperative morbidity. Despite this, the differences in comparing neostigmine/glycopyrrolate and sugammadex, such as BMI and comorbidities, were not identified on multivariate analysis to predict increased GI-2. We, therefore, postulate that these variables do not account for the differences in return of gastrointestinal function.

On multivariate linear regression analysis, bowel anastomoses formation, increased postoperative opioid use and neostigmine use were predictors for a prolonged time to achieving GI-2. Postoperative opioid use has clear associations with delayed return of gastrointestinal function, resulting in increased complications, length of hospital stay and hospital costs.[27, 100] Postoperative opioid use is a modifiable risk factor, with opioid avoidance strategies and interventions such as alvimopan, showing improvements in time to achieve GI-2.[250] Other studies have also demonstrated, as in our cohort, a link between anastomosis formation and delayed return of bowel function, likely due to increased

operative bowel handling.[84, 279] This is also supported by an open surgical approach being associated with delay in return of GI-2, although this did not reach significance on multivariate analyses.

For clinicians, the regular use of sugammadex over neostigmine/glycopyrrolate for neuromuscular reversal is hindered for a few key reasons. During the period of this study, the cost of sugammadex was AU$125 and neostigmine/glycopyrrolate was significantly cheaper at AU$3. The benefits of sugammadex outlined in previous studies and the current study do not outweigh the discrepancy in cost between the two medications.[280] A randomised-blinded study will be required to truly identify the impact sugammadex has on GI-2 and time to first stool. Should this demonstrate a significant clinical improvement in gastrointestinal function recovery, the regular use of sugammadex as part of an ERP could be economically justified, given the financial impact of POI.[261] Furthermore, sugammadex has the potential to cause anaphylaxis.[280] Although this is rare, neostigmine has no risk of anaphylaxis. Given the financial cost of sugammadex and the risk of anaphylaxis, the use of sugammadex for patients remains judicious.

This study had several limitations. This study was retrospective in design. Although there was an attempt to reduce bias by using consecutive patients with strict inclusion and exclusion criteria, all selection biases cannot be eliminated. Also, some data points were missing. The baseline characteristics between sugammadex and neostigmine patients differed due to anaesthetist selection based on patient factors. Furthermore a propensity-matched analysis was unable to be performed, as the ratio of the number of relevant predictive variables to the total number of patients in the denominator was too high to present a meaningful analysis. To assess the effects of acetylcholinesterase inhibitors on the development of POI, we are currently recruiting for a double blinded randomised

controlled trial using postoperative acetylcholinesterase inhibitors (pyridostigmine) to investigate this question further (ACTRN:12621000530820).

4.6 CONCLUSION

This dataset forms the largest cohort of colorectal patients investigating the impact of neostigmine/glycopyrrolate and sugammadex use as neuromuscular reversal agents against the validated outcome of GI-2. Sugammadex use was associated with a shorter time to first stool and GI-2. However, the selection of neuromuscular reversal agents had no significant clinical impact on the development of POI. On multivariate analysis, neostigmine use, bowel anastomoses and increased postoperative opioid use were associated with delayed achievement of GI-2.

CHAPTER 5: COST OF POSTOPERATIVE ILEUS FOLLOWING COLORECTAL SURGERY: A COST ANALYSIS IN THE AUSTRALIAN PUBLIC HOSPITAL SETTING.

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Colorectal Dis 2022; June 23. https://doi.org/10.1111/codi.16235

Statement of Authorship

Title of Paper	Cost of postoperative ileus following colorectal surgery: A cost analysis in the Australian public hospital setting.
Publication Status	Published
Publication Details	Traeger L, Koullouros M, Bedrikovetski S, Kroon HM, Thomas ML, Moore JW, Sammour T. Cost of postoperative ileus following colorectal surgery: A cost analysis in the Australian public hospital setting. Colorectal Dis. 2022 Nov;24(11):1416-1426. https://doi.org/10.1111/codi.16235.

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Name of Principal Author (Candidate)	Luke Traeger		
Contribution to the Paper	Conceptualization; investigation; validation; analysis; writing original draft.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/10/2023

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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To evaluate the cost-effectiveness of future successful interventions, it was essential to consider the financial impact of POI. This study focused on the local context, providing insights into the financial implications of POI in an Australian institution. Unlike previous global literature, which uses ICD-9 codes to diagnose POI, our study uses a strict clinical definition, GI-2, to accurately identify POI.

5.1 ABSTRACT

Background: Postoperative ileus (POI) following surgery results in significant morbidity, drastically increasing hospital costs. As there are no specific Australian data, this study aimed to measure the cost of POI after colorectal surgery in an Australian public hospital.

Methods: A cost analysis was performed, for major elective colorectal surgical cases between 2018 and 2021 at the Royal Adelaide Hospital. POI was defined as not achieving GI-2, the validated composite measure, by postoperative day 4. Demographics, length of stay and 30-day complications were recorded retrospectively. Costings in Australian Dollars were collected from comprehensive hospital billing data. Univariate and multivariate analyses were performed.

Results: Of the 415 patients included, 34.9% (n=145) developed POI. POI was more prevalent in males, smokers, previous intra-abdominal surgery, and converted laparoscopic surgery ($p<0.05$). POI was associated with increased length of stay (8 vs. 5 days, $p<0.001$) and with higher rates of complications such as pneumonia (15.2% vs. 8.1%, $p=0.027$). Total cost of inpatient care was 26.4% higher after POI (AU$37,690 vs. AU$29,822, $p<0.001$). POI was associated with increased staffing costs, as well as diagnostics, pharmacy, and hospital services. On multivariate analysis POI, elderly patients, stoma formation, large bowel surgery, prolonged theatre time, complications and length of stay were predictive of increased costs ($p<0.05$).

Conclusion: In Australia, POI is significantly associated with increased complications and higher costs due to prolonged hospital stay and increased healthcare resource utilisation. Efforts to reduce POI rates could diminish its morbidity and associated expenses, decreasing the burden on the healthcare system.

5.2 INTRODUCTION

One of the most frequent and morbid complications following abdominal surgery is postoperative ileus (POI), resulting from impaired gastrointestinal transit.[252] The principal features of POI include distention of the abdomen, intolerance of oral intake, nausea and vomiting, and absence of flatus or stool.[128] Reported incidences of POI range between 7-27%, even in the setting of enhanced recovery protocols.[17, 100, 281] The highest incidence of POI is seen after colorectal surgery, due to multiple patient-related, operative and postoperative factors.[17, 63, 84, 100, 101] Colorectal surgery specific factors such as handling of the bowel, splenic flexure mobilisation, stoma formation, open approach and rectal resections are known to predispose to POI.[63, 101, 102]

POI increases the risk of pneumonia, and the delay of adequate nutritional intake contributes to wound healing impairment and anastomotic failure.[12, 128] Furthermore, POI leads to higher risk of organ failure (such as renal and hepatic failure), prolongs hospital stay and increases 30-day readmission and mortality rates.[12, 128] Furthermore, delayed gastrointestinal recovery such as uncomplicated POI, directly impedes recovery of patient autonomy and subsequent discharge.[9] Preventing POI from occurring could reduce delayed discharges by 33%, readmissions by 21% and mortality by 20%.[12]

The morbidity associated with POI leads to a significant financial burden on healthcare systems. Previous studies have demonstrated a >50% increase in hospital costs related to additional expenses for medical, nursing, allied health, radiology and pharmacy services. POI as a single complication is estimated to cost over US$750 million per year in the US alone.[27-29, 126, 127] To date, no Australian POI cost reports have been published. Therefore, the aim of this study was to investigate the financial implications of POI after colorectal surgery in a public hospital in Adelaide, Australia.

5.3 METHODS

This study is reported using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines (Appendix C)[282] and was approved by the Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee.

5.3.1 PATIENT SELECTION AND DEFINITIONS

This is a single-centre retrospective study performed at the Royal Adelaide Hospital (RAH), Australia. The RAH Colorectal Unit performs over 300 major colorectal procedures per year. The RAH is one of four major public hospitals in South Australia performing colorectal surgery with colorectal specialists. Considered for inclusion were patients operated electively between February 2018 and March 2021 who were identified from the Department's admission lists. POI was defined using the validated composite score GI-2, a measure of passage of stool and 24-hour tolerance of oral diet.[25] GI-2 was calculated retrospectively from medical records, for analysis. POI was defined as a patient not achieving GI-2 by postoperative day four, based on the definition by Vather et al.[4] Patient discharged prior to achieving GI-2 were considered to not have POI. Diagnosis was corroborated with established prospective morbidity audits. All patients at the RAH, are placed on an enhanced recovery pathway (ERP). Patients undergoing colonic resections receive bowel preparation with the addition of a sodium phosphate (Fleet®; Prestige Consumer Healthcare Inc., Lynchburg, Virginia, USA) enema on admission, with left sided resections not receiving an enema. The ERP protocol is provided in Appendix C.

5.3.2 INCLUSION AND EXCLUSION CRITERIA

Patients 18 years and older, undergoing elective major bowel surgery involving large bowel resections, and formation or closure of stoma were included. Patients were excluded if they underwent emergency surgery or minor elective surgery such as

examination under anaesthesia, appendicectomy, haemorrhoidectomy or fistula surgery. Small bowel resections were excluded to focus on colorectal procedures and reduce heterogeneity of the data. Pelvic exenterations were also excluded due to increased morbidity and length of stay that would skew the data and make it less generalisable to other public hospital settings. Robotic cases were excluded as they are performed offsite and transferred to the RAH for postoperative care, making cost analysis between the two sites unreliable. Patient selection is displayed in Figure 7.

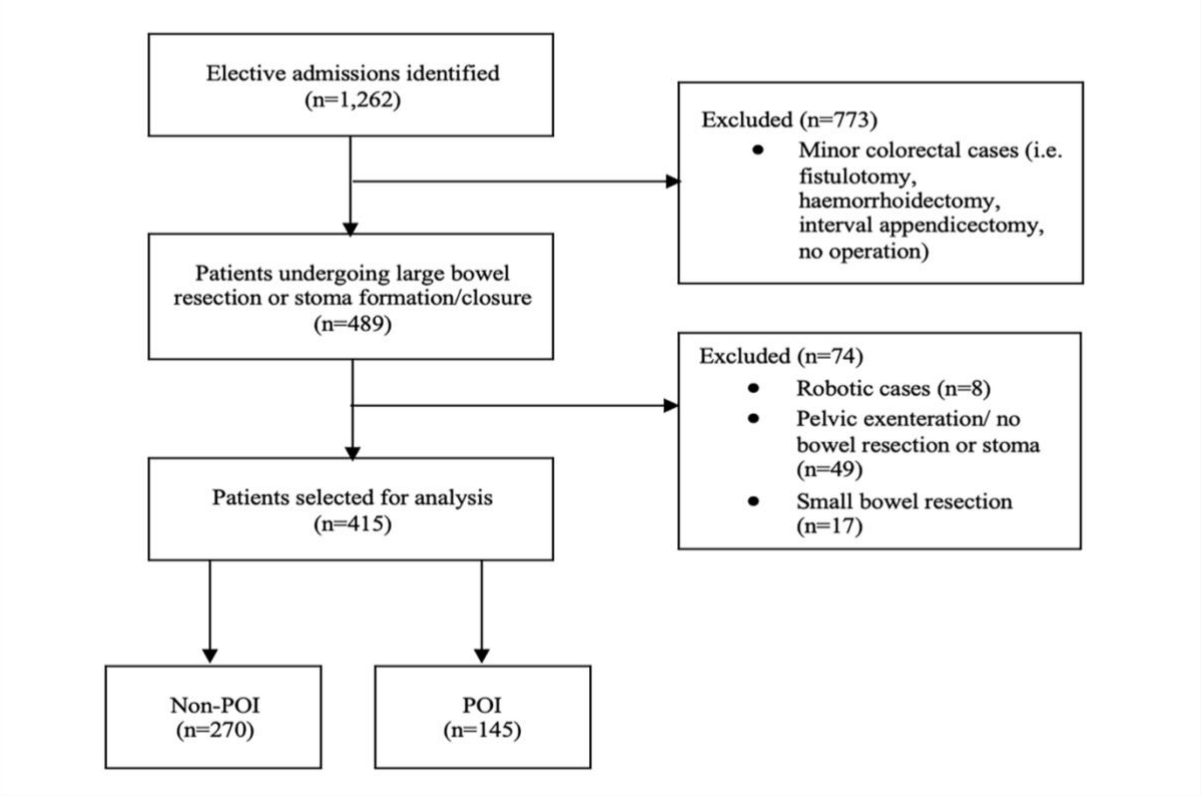

Figure 7. Flow-chart of patient selection for patients between February 2018 and March 2021.

5.3.3 DATA COLLECTION

Data was collected from admission records, prospective morbidity and mortality audits and from electronic and paper medical records, based on known risk factors for POI from the literature.[17, 63, 101] Baseline data that was collected included age, gender, body mass index (BMI), smoking history, congestive cardiac failure (CCF) within the last 30 days, chronic obstructive pulmonary disease (COPD), hypertension requiring medication, diabetes mellitus and previous abdominal surgery. Other preoperative variables included haemoglobin and albumin levels. Intraoperative data included the diagnosis (benign or malignant), approach of surgery (open/laparoscopic), conversion from laparoscopic to open, procedure type, incidence and type of stoma, and duration in theatre. Data on use of patient controlled analgesia (PCA), transversus abdominis plane (TAP) catheters, as well as intraoperative and postoperative day one to four use of opioids in morphine equivalents was collected. Postoperative outcomes included intensive care admission, return to theatre, length of stay, thirty-day complications, Clavien-Dindo (CD) grades, and readmission rates.[273]

5.3.4 OUTCOMES

The primary outcome was the total cost of inpatient stay per patient in Australian dollars (AU$). Costs were adjusted to 2021 Australian dollars for consumer price inflation (~0.86-4.54% over the study period).[283] Subgroup analyses were performed for the total cost of inpatient stay excluding ‘fixed’ costs of theatre, depreciation and non-clinical costs, as these do not reflect the cost of ileus per se, to identify the attributable medical costs of POI. Total inpatient cost per patient excluding CD grade $\geq$3 complications, was performed to attempt to identify POI attributable costs without significant surgical complication. Subgroup analysis was also performed on expenses for medical, nursing and allied health staff, critical care, theatre, imaging, pathology, pharmacy, supplies, hospital services, non-

clinical and depreciation individually. Explanation and definitions of these costs is provided in Appendix C. Individual patient costs, separated into expenses per category were received from billing data by the Business Intelligence and Performance Reporting Unit, CALHN. These costs represent hospital costs per patient, prior to reimbursement from private insurers.

5.3.5 STATISTICAL ANALYSIS

Patients with and without POI were compared, and cost of POI per patient was calculated. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics are reported as mean (SD) or median (IQR [range]) for continuous variables and categorical variables as frequency (percentage). Categorical variables were analysed using the Fisher's exact (when $n<5$) and Chi-squared tests. Continuous variables were analysed with the Student t-test or Mann–Whitney U-test depending on the normality of the data (Shapiro-Wilk test). Costs were presented as mean (SD), as per the CHEERS guidelines.[282] Univariate and multivariate linear regression analyses were performed on variables chosen *a-priori* on log-normal transformed total cost of inpatient stay, to determine independent predictors of total cost of inpatient stay. Statistical significance was accepted at $p<0.05$.

5.4 RESULTS

Financial costing data were retrieved for all 415 eligible patients undergoing elective surgery in the study period, of whom 145 (34.9%) experienced POI. Patients who suffered POI were more frequently male, active or ex-smokers, and more had previous abdominal surgery ($p<0.05$ for all characteristics). POI patients also underwent laparoscopic converted to open surgery more frequently (30.6% vs. 10.7%, $p<0.001$) and underwent reversal of Hartmann's procedure or reversal of ileostomy and abdominoperineal resection

more commonly (p=0.041). Patients suffering POI were more likely to have an increase in theatre time (163.0 vs. 147.5 minutes, p=0.021), and increased amount of postoperative day one to four analgesia given (119.25 vs 120.0 MEQ, p<0.001). Patients participating in the STIMULAX and PyRICo-P trials at our institution had equal distribution between non-POI and POI groups.[235, 249] These and other baseline characteristics and differences between the POI and non-POI groups are presented in Table 11.

Table 11. Comparison of baseline patient characteristics and operative data.

Variable	Non-POI (n=270)	POI (n=145)	p- value
Age; y	64 (52-73 [18-92])	66 (58-74 [20-94])	0.121
Gender			**0.021**
Female	121 (44.8%)	48 (33.1%)	
Male	149 (55.2%)	97 (66.9%)	
ASA			0.714
I	7 (2.6%)	3 (2.1%)	
II	137 (50.7%)	66 (45.0%)	
III	123 (45.6%)	74 (51.0%)	
IV	3 (1.1%)	2 (1.4%)	
Smoking history			**0.015**
Active	47 (17.4%)	33 (22.8%)	
Ex-smoker (>6 weeks)	86 (31.9%)	60 (41.4%)	
BMI; kg/m^2	27.1 (23.9-31.2 [15.9 – 58.8])	27.3 (24.5-31.9 [15.9 – 63.7])	0.266
CCF within last 30 days	6 (2.2%)	4 (2.8%)	0.745
COPD	17 (6.3%)	17 (11.7%)	0.055
Hypertension requiring medication	111 (41.1%)	70 (48.3%)	0.161
Diabetes mellitus			0.546
Prescribed tablets	58 (21.5%)	27 (18.6%)	
Prescribed insulin	2 (0.7%)	0 (0.0%)	
Undergone previous abdominal surgery	151 (55.9%)	102 (70.3%)	**0.004**
Preoperative haemoglobin; g/L	136 (123-145 [81-178])	136 (123-149 [82-176])	0.442
Missing	*0*	*1*	
Preoperative albumin; g/L	37 (34-40 [19-49])	37 (34-39 [20-49])	0.932
Missing	*7*	*8*	
Malignancy diagnosed	150 (55.6%)	75 (51.7%)	0.455
Surgical approach			0.282
Open	121 (44.8%)	73 (50.3%)	
Laparoscopic	149 (55.2%)	72 (49.7%)	
Conversion from laparoscopic to open procedure	16 (10.7%)	22 (30.6%)	**<0.001**
Operations			**0.041**
Right sided (Ileocolic resection, extended/right hemicolectomy, transverse colectomy, subtotal colectomy)	92 (34.1%)	52 (35.9%)	
Left sided (Left hemicolectomy, sigmoidectomy, anterior resection)	85 (31.5%)	38 (26.2%)	
Total colectomy, pan- proctocolectomy, completion colectomy	22 (8.1%)	5 (3.4%)	
Reversal of Hartmann's procedure	19 (7.0%)	18 (12.4%)	
Reversal of ileostomy	40 (14.8%)	27 (18.6%)	
Abdomino-perineal resection	1 (0.4%)	3 (2.1%)	
Formation of stoma	11 (4.1%)	2 (1.4%)	
Stoma formed	59 (21.9%)	25 (17.2%)	0.265
Stoma type			0.416
Ileostomy	43 (72.9%)	16 (64.0%)	
Colostomy	16 (27.1%)	9 (36.0%)	
Theatre time; mins	147.5 (109.0-193.5 [29.0-433.0])	163.0 (128.0-214.0 [45.0-385.0])	**0.021**
Intraoperative and recovery opioid use; MEQ	120.0 (91-157.5 [20.0-806.0])	126.0 (90.4-169.5 [20.0-385.0])	0.200
Total opioid use POD 1-4; MEQ	120.0 (54.25-229.0 [0-1208.0])	199.25 (99.75-394.88 [0-1821.2])	**<0.001**
PCA	54 (25.2%)	36 (30.8%)	0.279
Missing	*56*	*28*	
TAP catheters	83 (43.5%)	58 (54.2%)	0.075

Missing	*79*	*33*	
STIMULAX/PyRICo-P Trial [235, 249]	102 (37.8%)	51 (35.2%)	0.600

[a]n=149 for non-POI; n=72 for POI.
Values are median (IQR [range]), mean (SD) or number (proportion).

Table 12 shows the comparison of postoperative outcomes and complications between the two groups. The non-POI group had a median length of stay of 5 (IQR(3-7), Range [1-47]) days compared to 8 (IQR(6-11), Range [3-60]) days in the POI group ($p<0.001$). Patients diagnosed with POI required total parenteral nutrition more frequently (3.4% vs. 0.4%, $p=0.021$). Patients with POI had higher CD complication grades, mostly CD II, compared to patients without POI ($p<0.001$). When excluding POI as a complication, the statistical difference in highest CD complication grade remained ($p=0.016$). Patients diagnosed with POI had more urinary tract infections (6.2% vs. 1.1%, $p=0.005$), pneumonia or respiratory failure (15.2% vs. 8.1%, $p=0.027$), cardiac complications (7.6% vs. 1.5%, $p=0.004$) and deep vein thrombosis or venous thromboembolisms (2.8% vs. 0.4%, $p=0.053$).

Table 12. Comparison of 30-day outcome and complication data.

Variable	Non-POI (n=270)	POI (n=145)	p-value
GI-2	3 (2-4 [0-4])	6 (5-7 [3-12])	**<0.001**
ICU admission required	9 (3.3%)	11 (7.6%)	0.054
Transfusion required	8 (3.0%)	7 (4.8%)	0.332
Required total parental nutrition	1 (0.4%)	5 (3.4%)	**0.021**
Return to theatre	13 (4.8%)	8 (5.5%)	0.756
Readmission	16 (5.9%)	15 (10.3%)	0.103
Length of stay; d	5 (3-7 [1-47])	8 (6-11 [3-60])	**<0.001**
Highest CD grade			**<0.001**
No complication	159 (58.9%)	0 (0.0%)	
1	44 (16.3%)	0 (0.0%)	
2	49 (18.1%)	125 (86.2%)	
3	7 (2.6%)	8 (5.5%)	
4a	6 (2.6%)	8 (5.5%)	
4b	1 (0.4%)	3 (2.1%)	
5	4 (1.5%)	1 (0.7%)	
Highest CD grade excluding POI			**0.016**
No complication	159 (58.9%)	65 (44.8%)	
1	44 (16.3%)	22 (15.2%)	
2	49 (18.1%)	38 (26.2%)	
3	7 (2.6%)	8 (5.5%)	
4a	6 (2.2%)	8 (5.5%)	
4b	1 (0.4%)	3 (2.1%)	
5	4 (1.5%)	1 (0.7%)	
Complications			
Anastomotic leak[1]	13 (5.3%)	10 (7.4%)	0.400
Wound dehiscence/infection	16 (5.9%)	11 (7.6%)	0.513
Urinary retention	5 (1.9%)	4 (2.8%)	0.725
Urinary tract infection	3 (1.1%)	9 (6.2%)	**0.005**
Pneumonia/respiratory failure	22 (8.1%)	22 (15.2%)	**0.027**
Cardiac complication	4 (1.5%)	11 (7.6%)	**0.004**
DVT/VTE	1 (0.4%)	4 (2.8%)	0.053
High stoma output[2]	7 (11.9%)	5 (20.0%)	0.330
Sepsis	7 (2.6%)	5 (3.4%)	0.620
Electrolyte disturbance	29 (10.7%)	20 (13.8%)	0.358

[1]n=247 Non-POI patients had an anastomosis; n=135 POI patients had an anastomosis. [2]n=59 Non-POI patients had a stoma; n=25 POI patients had a stoma.
Values are median (IQR [range]), mean (SD) or number (proportion).

Table 13 demonstrates the difference in cost of inpatient stay. The POI group had a significantly higher mean total cost of inpatient stay of AU$37,689.87 per patient compared to the non-POI group of AU$29,821.70 ($p<0.001$), a 26.4% or AU$7,868.17 increase in total cost. Individual breakdown of cost demonstrated increased expenses of medical, nursing and allied health in the POI group. Pharmacy, supplies, hospital services, and non-clinical costs were also significantly higher in the POI group. When excluding theatre, depreciation and non-clinical costs there was a 44.5% (AU$6,174.13) increase in cost in the POI group (AU$20,059.16 vs. AU$13,885.03, $p<0.001$). When analysing the total cost of inpatient stay, excluding patients with CD grade >3 complications, there was a 27% (AU$7,159) increase in patients with POI.

Table 13. Cost of inpatient stay.

	Non-POI (n=270)	POI (n=145)	% difference	p- value
Total inpatient costs per patient	$29,821.70 ($20,410.18)	$37,689.87 ($21,586.73)	26.4% increase	**<0.001**
Total inpatient costs per patient excluding theatre, depreciation and non-clinical costs	$13,885.03 ($15,177.31)	$20,059.16 ($16,377.75)	44.5% increase	**<0.00**1
Total inpatient costs per patient excluding CD grade > 3 [1]	$26,544.25 ($13,993.92)	$33,703.30 ($15,826.06)	27.0% increase	**<0.00**1
Costing breakdown				
Medical staff	$1,774.26 ($2,168.99)	$2,549.24 ($1,943.36)	43.7% increase	**<0.001**
Nursing staff	$4,358.33 ($4,172.85)	$6,143.79 ($4,068.43)	41.0% increase	**<0.001**
Allied health staff	$206.59 ($577.99)	$470.15 ($1,143.10)	127.6% increase	**0.002**
Indirect salary costs	$2,540.99 ($1,959.57)	$3,301.39 ($2,257.06)	29.9% increase	**<0.001**
Critical care[2]	$13,986.17 ($10,802.94)	$12,056.36 ($7,801.33)	13.8% decrease	0.527
Theatre	$12,820.12 ($6,043.31)	$13,724.76 ($5,856.68)	7.1% increase	0.142
Imaging[3]	$786.68 ($1,129.06)	$809.88 ($837.29)	2.9% increase	0.890
Pathology[4]	$864.86 ($828.12)	$977.97 ($732.03)	13.1% increase	0.198
Pharmacy	$323.13 ($734.37)	$510.85 ($756.77)	58.1% increase	**0.014**
Supplies	$1,894.70 ($1,836.70)	$2,697.42 ($1,756.76)	42.4% increase	**<0.001**
Hospital services	$950.50 ($826.69)	$1,246.59 ($832.12)	31.2% increase	**<0.001**
Non-clinical	$588.75 ($487.78)	$788.43 ($464.97)	33.9% increase	**<0.001**
Depreciation	$2,464.76 ($1,502.81)	$2,998.56 ($1,557.07)	21.7% increase	**<0.001**

Data presented in 2021 Australian dollars, adjusted for inflation.
[1]n=252 Non-POI patients after excluding CD grade >3; n = 125 POI after excluding CD grade >3. [2]n=17 Non-POI patients receiving critical care; n = 21 POI patients receiving critical care. [3]n=66 Non-POI patients receiving imaging; n=77 POI patients receiving imaging. [4]n=227 Non-POI patients who had pathology; n = 129 POI patients who has pathology. P-value calculated for whole patient cohort.
Values are presented as mean (SD).

Table 14 displays the results of the multivariate analysis. On multivariate linear regression analysis age ≥65 years old (p=0.032), large bowel surgery (p=0.001), stoma formation (p<0.001), duration of theatre (>150 mins) (p<0.001), POI (p=0.034), CD grade ≥3 (p=0.002), and prolonged length of hospital stay ≥ 6 days (p<0.001) were independently predictive of a total increased cost of stay.

Table 14. Multivariate linear regression analysis on total cost of inpatient stay.

Variable	n (%)	Cost	Univariate	Multivariate
Age ≥65			**0.025**	**0.032**
Yes	209 (50.4%)	$34,293.95 ($21,355.55)		
No	206 (49.6%)	$30,822.60 ($20,823.36)		
Gender			0.382	0.366
Female	169 (40.7%)	$31,873.34 ($21,542.68)		
Male	246 (59.3%)	$33,049.98 ($20,888.02)		
ASA ≥3			**0.005**	0.506
Yes	202 (48.7%)	$35,257.79 ($23,586.06)		
No	213 (51.3%)	$30,022.61 ($18,215.55)		
BMI >30			**0.008**	0.654
Yes	136 (32.8%)	$34,827.47 ($18,915.94)		
No	279 (67.2%)	$31,470.80 ($22,090.90)		
Smoking history			0.079	0.956
Yes	226 (54.5%)	$34,406.80 ($23,965.21)		
No	189 (45.5%)	$30,375.41 ($16,964.27)		
Undergone previous abdominal surgery			0.773	0.633
Yes	253 (61.0%)	$33,770.29 ($24,450.90)		
No	162 (39.0%)	$30,697.57 ($14,405.69)		
Conversion from laparoscopic to open procedure			**<0.001**	0.115
Yes	38 (16.1%)	$39,611.39 ($15,469.54)		
No	199 (83.9%)	$29,813.71 ($13,011.43)		
Stoma performed			**0.001**	**<0.001**
Yes	85 (20.5%)	$36,443.98 ($17,871.80)		
No	330 (79.5%)	$31,573.19 ($21,814.91)		
Operation type			**<0.001**	**0.001**
Large Bowel	348 (83.9%)	$34,070.32 ($19,430.40)		
Reversal of ileostomy	67 (16.1%)	$24,918.94 ($27,211.30)		
Duration of theatre (median >150 mins)			**<0.001**	**<0.001**
Yes	215 (51.8%)	$38,710.15 ($21,510.46)		
No	200 (48.2%)	$25,971.04 ($18,643.47)		
POI			**<0.001**	**0.034**
Yes	145 (34.9%)	$37,689.87 ($21,586.73)		
No	270 (65.1%)	$29,821.70 ($20,410.18)		
Total opioid use POD 1-4 (>median 150 MEQ)			**<0.001**	0.672
Yes	197 (48.4%)	$35,761.70 ($20,606.44)		
No	210 (51,6%)	$29,824.25 ($21,617.57)		
TAP catheters			**0.013**	0.581
Yes	141 (47.3%)	$32,573.31 ($15,484.46)		

No	157 (52.7%)	$30,380.62 ($22,636.61)		
CD grade (≥3)			**<0.001**	**0.002**
Yes	38 (9.2%)	$68,811.22 ($35,094.29)		
No	377 (90.8%)	$28,917.94 ($14,990.53)		
ICU admission			**<0.001**	0.051
Yes	20 (4.8%)	$83,702.53 ($38,711.59)		
No	395 (95.2%)	$29,981.87 ($16,057.59)		
Required total parental nutrition			**<0.001**	0.848
Yes	6 (1.4%)	$66,655.11 ($48,114.74)		
No	409 (98.6%)	$32,070.80 ($20,192.29)		
Urinary tract infection			**0.028**	0.126
Yes	12 (2.9%)	$41,754.25 ($19,159.66)		
No	403 (97.1%)	$32,297.37 ($21,155.72)		
Anastomotic leak			**<0.001**	0.280
Yes	23 (6.0%)	$66,127.23 ($33,792.25)		
No	359 (94.0%)	$30,891.49 ($18,897.74)		
Pneumonia/ respiratory failure			**<0.001**	0.447
Yes	44 (10.6%)	$53,309.42 ($36,277.94)		
No	371 (89.4%)	$30,111.25 ($17,024.71)		
Cardiac complication			**0.016**	0.645
Yes	15 (3.3%)	$41,224.18 ($16,384.21)		
No	400 (96.4%)	$32,246.32 ($21,244.35)		
DVT/VTE			**0.001**	0.147
Yes	5 (1.2%)	$65,978.87 ($37,488.37)		
No	410 (98.8%)	$32,163.40 ($20,609.96)		
Length of Stay			**<0.001**	**<0.001**
≥6 days	227 (54.7%)	$41,255.42 ($24,856.28)		
<6 days	188 (45.3%)	$22,120.85 ($6,474.03)		

Data presented in 2021 Australian dollars, adjusted for inflation.
Presented as mean (standard deviation) and number (frequency).

5.5 DISCUSSION

This study confirms that in Australia, as also reported internationally, the financial burden of POI is significant, increasing total hospital cost per patient by 26.4%. This is a result of significant increases in length of hospital stay and more complications suffered by POI patients.

The 34.9% POI rate in our study is higher than in previous reports (8.5-27%)[27-29, 126, 127], which could reflect the different POI definitions used, the inclusion of minor procedures in other studies, and under-reporting of POI. This may reflect that fact that many of the patients in the current study participated in clinical trials[235, 249] specifically investigating POI (an interest of our research group), the strict POI definition used according to GI-2, and the fact that complications in our Department are recorded prospectively. Mao et al. reported a POI rate of 27%, also using strict criteria of symptoms for POI diagnosis such as nausea or vomiting, tolerance of solid diet, abdominal distension, absence of flatus and stools, and radiological evidence on X-ray or computed tomography.[126] Their POI rate is comparable to that of the current study, likely reflecting the prospective collection and similar detailed definition of POI. Studies using GI-2 to define POI following colorectal surgery, have reported rates of 10.1-28.8%.[130, 284] This rate differs from our reported rate, possibly due to the exclusion of patients receiving a stoma[130] and benign procedures in these other studies.[284] Other costing papers have reported lower POI rates of 8.5-24%, however, often collected retrospectively and using ICD-9 diagnostic codes rather than using clinical signs and symptoms to diagnose POI, leading to potential for underestimation of POI rate and the associated financial burden.[27-29, 127] Also, these papers reported on a mix of surgical procedures, altering the risk of POI and its reported frequency. Of note, 40.3% of the patients in the current study experienced POI following reversal of ileostomy. Although the study aim was not to identify the incidence of POI following reversal of ileostomy, this is a

considerably higher rate than the pooled estimate of 12.4% (95%CI 9.2–16.5%; I_2 = 79%) by Garfinkle et al.[285] The eight studies included in their review, used a variety of POI definitions and did not use GI-2, thus highlighting that variations in definition can substantially alter the incidence of POI.

Variables previously shown to impact the development of POI such as ASA, malignancy status, stoma formation, preoperative haemoglobin and albumin levels, and intensive care unit admission did not reach significance in our cohort.[17, 63, 101] We suspect that this is the result of the wide range of definitions for POI used in previous studies. The validated GI-2 composite measure more uniformly diagnoses POI and provides better opportunities to compare study outcomes. The literature reported increase in total hospital cost of 48.4-99.5% because of POI is larger than seen in our study (26.4%).[27-29, 126, 127] This may be due to the other studies not using the CHEERS[282] guidelines, potentially leading to overestimation of costs. However, when excluding 'fixed' costs of theatre, depreciation and non-clinical costs to ascertain the postoperative medical costs, we demonstrated a 44.5% increase in cost of inpatient stay, which is more in line with the literature. In comparison, Australia's public funding model is similar to that of New Zealand, where a single centre study reported a total cost increase of 71%, considerably larger than our results.[126] This is despite the similar rate of CD grade $\geq$3 (13.8%) of the current study compared to the 12% reported in their study.[126] When excluding CD grade >3 complications, to attempt to exclude other significant surgical complications, there was a 27% increase in total cost of inpatient stay for patients with POI. However, as POI often occurs in conjunction with other complications, this does not allow us to truly identify the cost of POI.

In the current study, the major cause of increased costs due to POI relates to the three days longer length of stay. This is in line with previous POI studies reporting an increased

median length of stay of 4.9-7.5 days, significantly increasing medical and nursing staff costs.[27-29, 126, 127] Other factors increasing the cost of hospital stay include a higher demand for imaging to confirm the diagnosis or to investigate factors such as anastomotic leakage resulting in septic ileus or to diagnose POI-related complications such as pneumonia. Higher pharmacy costs were also noted, likely due to increased service requirement and greater opioid prescribing, which has previously been demonstrated.[27] It is well established, and reaffirmed in this study, that patients with POI are predisposed to other complications such as pneumonia, deep vein thrombosis and cardiac events.[12, 128] These POI-related complications have an additional considerable impact on cost. Although trying to isolate the costs of POI separately from other complications could be technically possible, it would be clinically irrelevant as these other complications coincide with POI. Costing data for other complications were therefore not adjusted. This allowed the current study to be a true representation of the overall clinical cost of POI.

In South Australia, for patients electing to use private hospital cover in a public hospital, gaps or excess charges are waived. We are therefore able to report the cost prior to reimbursement from private insurers from a single centre-public hospital analysis in South Australia. Given the differences between state and territories state/government reimbursement schemes across the country, the data from the current study are indicative of the cost of POI at a hospital level prior to reimbursement and could therefore be generalisable to hospitals throughout Australia.

In the univariate and multivariate linear regression analyses, older patients ($p=0.032$), patients who had a stoma formed ($p<0.001$), large bowel operations ($p=0.001$), prolonged duration in theatre ($p<0.001$), prolonged length of hospital stay ($p<0.001$), CD grade $\geq$3 complications ($p=0.002$) and POI ($p=0.034$) were identified as independent predictors of

an increased total cost of inpatient stay. These results confirm previous findings, that increased health care resource utilisation by factors such as age and stoma formation increase the total cost of inpatient stay.[126, 286] Also, increased duration in theatre has been shown to increase POI rates, and associated complications[17, 84, 287], due to difficulty in the operation, such as adhesions or extensive disease.[84] Despite CD grade $\geq$3 complications being predictive of increased total cost of admission, individual complications such as anastomotic leak (p=0.280) or intensive care unit admission (p=0.051) were not identified as predictors of an increased total cost of hospital stay. We speculate that these findings are a result of POI rarely occurring in isolation without other complications. Furthermore, length of stay is strongly predictive of increased hospital costs, likely owing to delayed discharge secondary to complications such as POI contributing to a loss of patient autonomy.[9, 29, 126]

This study was limited by its retrospective design, with potential for selection or misclassification bias. To reduce this risk, patients were consecutively selected from the admission records, and complications were double checked via the prospectively collected Colorectal Unit morbidity and mortality audit in which GI-2 was used to classify POI. Highlighting a limitation of our definition of POI, 19 patients were discharged prior to achieving GI-2. These patients may have achieved GI-2 before postoperative day four, however this may have led to underestimation of POI. Furthermore, two patients who achieved GI-2 and were discharged on postoperative day 3, were shortly readmitted after discharge with POI requiring nasogastric decompression. Also, because of the time selected, there was differences in proportions of surgical procedures included, potential leading to recruitment bias. However, our cohort does represent the diverse elective work undertaken by our Colorectal Unit. Also, as this is a single-centre analysis, overall generalisability may be reduced. Despite the RAH being a major tertiary centre in South

Australia, to be able to map the full economic impact of POI in Australia, in future studies multiple sites with prospective data will be required.

5.6 CONCLUSION

This study shows that in an Australian institution, POI is associated with a significant increase in complications. POI was shown to be an independent predictor for increased total cost of hospital admission, along with age, stoma formation, prolonged length of stay and higher-grade complications. Efforts aimed at reducing POI rates could diminish its morbidity and associated expenses, decreasing the burden on healthcare.

CHAPTER 6: THE GLOBAL COST OF POSTOPERATIVE ILEUS FOLLOWING ABDOMINAL SURGERY: META-ANALYSIS.

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BJS Open. 2023 June 23. https://doi.org/10.1093/bjsopen/zrad054

Statement of Authorship

Title of Paper	The global cost of postoperative ileus following abdominal surgery: meta-analysis.
Publication Status	Published
Publication Details	Traeger L, Koullouros M, Bedrikovetski S, Kroon H, Moore J, Sammour T. The global cost of postoperative ileus following abdominal surgery: meta-analysis. BJS Open. 2023 https://doi.org/10.1093/bjsopen/zrad054

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Contribution to the Paper	Conceptualization; investigation; validation; analysis; writing original draft.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Our experience, highlighted in Chapter 6, provided local context on the substantial financial burden of POI. To further evaluate these findings and give a broader perspective, I report the first systematic review quantifying the global financial impact of POI following abdominal surgery. The study includes a comprehensive meta-analysis that synthesises the literature on the global financial implications of POI.

6.1 ABSTRACT

Background: Following abdominal surgery, postoperative ileus (POI) is a common complication significantly increasing patient morbidity and cost of hospital admission. This is the first systematic review, aimed at determining the average global hospital cost per patient associated with POI.

Methods: A systematic search of electronic databases was performed from 2000 to March 2023. Studies included compared patients undergoing abdominal surgery who developed POI to those who did not, focusing on costing data. The primary outcome was the total cost of inpatient stay. Risk of Bias was assessed using the Newcastle-Ottawa assessment tool. Summary meta-analysis was performed.

Results: Of the 2071 studies identified, 88 papers were assessed for full eligibility. The systematic review included nine studies (2005-2022), investigating 1,860,889 patients undergoing general, colorectal, gynaecological, and urological surgery. These studies showed significant variations in the definition of POI. Six studies were eligible for meta-analysis showing an increase of €8,233 (95%CI [5,176-11,290], $p<0.0001$, $I_2=95.5\%$) per patient with POI resulting in a 66.3% increase in total hospital costs (95%CI [34.8-97.9], $p<0.0001$, $I_2=98.4\%$). However, there was significant bias between studies. Five colorectal surgery specific studies showed an increase of €7,242 (95%CI [4,502–9,983], $p<0.0001$, $I_2=86.0\%$) per patient with POI resulting in a 57.3% increase in total hospital costs (95%CI [36.3–78.3], $p<0.0001$, $I_2=85.7\%$).

Conclusion: The global financial burden of POI following abdominal surgery is significant. While further multicentre data using a uniform POI definition would be useful, reducing the

incidence and impact of POI are a priority to mitigate healthcare-related costs, and improve patient outcomes.

6.2 INTRODUCTION

Patients are at risk of impaired gastrointestinal function following intra-abdominal surgery, frequently leading to postoperative ileus (POI). The resulting diet intolerance, abdominal distention, nausea and vomiting are uncomfortable and distressing for patients.[128] POI is also associated with significant morbidity such as pneumonia, delayed wound healing, increased risk of anastomotic failure and organ failure, which prolong the length of stay, increase 30-day readmission rates and carry a mortality risk.[17, 100, 128, 281] Depending on the type of surgery, the incidence of POI ranges from 7-27%, with colorectal surgery having the highest incidence, despite implementing enhanced recovery protocols (ERPs).[13, 17, 100, 128, 281] To improve current ERPs with the aim of reducing the incidence of POI, several novel therapies, such as alvimopan, and trials using laxatives have been investigated with varied success.[235, 250] Despite these efforts, however, incidences of POI remain high.[12, 128]

The cost of hospital admission approximately doubles regardless of the severity and type of complication following abdominal surgery.[129] As a result, in the Australian healthcare system in 2003-2004, an extra AU$460 million (16% of total expenditure on healthcare costs) was spent on complications.[7] In the United States(US), future expenditure on surgical healthcare is set to exceed US$1 Trillion by 2025, accounting for one-fourteenth of the US economy.[2] Unfortunately, surgical complications will contribute significantly to this financial burden.

The increased morbidity and prolonged hospital stay secondary to POI are significant contributors to the financial burden of complications on healthcare systems, as POI remains one of the most common complications after abdominal surgery. Previous studies have demonstrated a 50-100% increase in total hospital costs per patient due to increased staffing costs, imaging, pharmacy and laboratory services.[27-31, 125-127] In our own single-

centre experience, we found an approximate AU$8,000 (€5,000) increase in total hospital costs, amounting to a 26.4% increase in total hospital costs per patient after the development of POI.[261] International efforts to mitigate this cost are urgently needed. We aimed to undertake the first systematic review and meta-analysis to identify the costs attributable to POI for patients after intra-abdominal surgery and better understand the financial burden of POI on the healthcare system globally.

6.3 METHODS

This study was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42021275071) and is reported in adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix D).[267]

6.3.1 SEARCH STRATEGY

A systematic search was performed by two independent reviewers (LT and MK) of PubMed (2000-2023), OVID MEDLINE (2000-2023), EMBASE (2000-2023), Cochrane Library (2005-2023), Clinicaltrials.gov, and Cumulative Index of Nursing and Allied Health Literature (CIANHL) databases (2000-2023). Studies were included until the 9th of March 2023. Medical subject headings (MeSH) and keyword search terms related to ‘cost’, ‘economics’, ‘abdominal’, ‘surgery’, and ‘ileus’ were used. The search strategies are provided in Appendix D.

6.3.2 ELIGIBILITY CRITERIA

Studies were included for full-text review if they were related to POI following intra-abdominal surgery. Inclusion criteria were randomised controlled trials (RCTs) or non-RCTs, including human patients over 18 years of age undergoing abdominal surgery

diagnosed with POI, investigating the cost of POI. Articles were excluded if they were short communications, reviews, opinion pieces and case reports. Spinal surgery studies were also excluded as from the articles it was unclear if the surgery was performed via an intraperitoneal approach and/or there was a neurogenic cause of intestinal paralysis. Pancreatic studies were also excluded as it was unclear if delayed return of gastrointestinal function was related to delayed gastric emptying or POI. Finally, patient studies with a mechanical cause of bowel obstruction were also excluded.

6.3.3 STUDY SELECTION

Studies were selected using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Both reviewers individually screened titles and abstracts. The reference lists of the articles that were reviewed full text were also checked to identify potential additional articles. Any disagreements were resolved by consensus arbitrated by a third author (SB).

6.3.4 DATA EXTRACTION AND SYNTHESIS

Two reviewers (LT and MK) extracted the data independently using a predefined standard data extraction form. Extracted baseline data included author name, country, year, study design, patient population, surgery type, number of patients, definition of POI, and incidence of POI.

6.3.5 RISK OF BIAS IN INDIVIDUAL STUDIES

Risk of bias was recorded using the Newcastle Ottawa scale and was tabulated, assessed by LT and MK.[288] A rating of 0 to 9 was allocated to each study, using parameters of patient selection, comparability of the study groups and outcomes reported. Good quality studies had a score ≥7.

6.3.6 OUTCOMES AND STATISTICAL ANALYSIS

The primary outcomes extracted included total hospital cost. The currency of total hospital cost and percentage change between the POI and non-POI groups was recorded. Secondary outcomes included total hospital costs per department. Data were corroborated following extraction and any discrepancies in the extracted data were resolved by the third reviewer (SB). Descriptive statistics were used for individual patient data analysis. No assumptions for missing data were made. Costing data were adjusted to Euros (€) for 2021. Costs were adjusted for consumer price inflation dependent on the study countries.[283, 289, 290] Exchange rates were taken on 31/12/2021.[291]

Summary statistics (mean (standard deviation)) were provided or able to be extracted from the included studies.[292-294] For analysis, mean difference and standard error was calculated using MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium). Summary meta-analysis of data was performed using StatsDirect software Version 3 (StatsDirect Ltd, Birkenhead, Wirral, United Kingdom). Results are presented as total pooled mean difference in total cost (€), with 95% confidence intervals (95%CI) and forest plots. For overall effect $p<0.05$ was considered statistically significant. Heterogeneity was estimated using Cochran's Q test and I_2 and was considered statistically significant when $p<0.05$ for the Cochran's Q test and $I_2>50\%$. Given the heterogeneity of the data, random weights were used for pooled meta-analyses. Risk of bias was analysed using the Eggar method, in which $p<0.05$ indicated significant bias.

6.4 RESULTS

The literature search identified 2,071 studies of which 953 were duplicates and were removed. Of the 1,118 studies screened for title and abstract, 1,030 were irrelevant.

Eighty-eight studies were screened in full-text review, with nine studies meeting the inclusion criteria (Figure 8).[27-31, 125-127, 261]

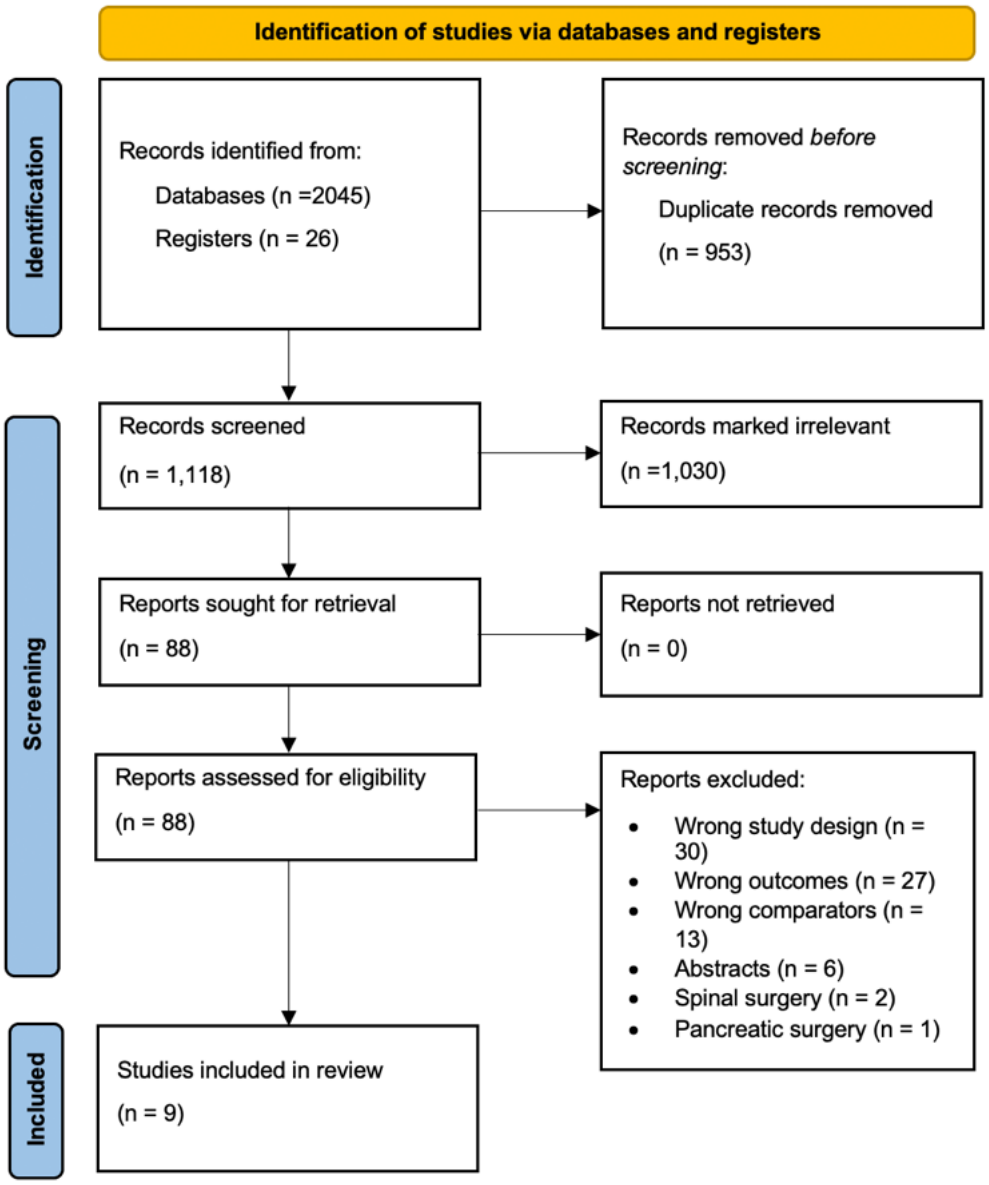

Figure 8. PRISMA flow chart.

6.4.1 CHARACTERISTICS OF STUDIES

The nine included studies came from four countries and were published between 2005 and 2022. They included a total of 1,860,889 patients, undergoing a range of procedures from general surgical, colorectal, gynaecological, and urological surgery.[27-31, 125-127, 261] No studies were randomised. Seven studies[27-31, 127, 261] were retrospective in design and two studies[125, 126] contained prospectively collected data. The complete study characteristics are provided in Table 15.

6.4.2 SURGICAL PROCEDURES

The included studies explored the cost of POI in a wide variety of surgeries, summarised in Table 15. Five studies reported colorectal surgical procedures alone,[29, 125-127, 261] two studies reported gynaecological, general surgical and colorectal cases together[28, 31], one study reported colorectal and general surgical cases.[27] One study explored urological cases.[30] Six studies investigated open and laparoscopic approaches to surgery.[27, 29, 125-127, 261] One studies investigated open surgical approach[30] and in two studies the surgical approach was unclear.[28, 31] Four studies had postoperative care guided by an ERP [125-127, 261], and five studies did not state if an ERP was used postoperatively.[27-31]

Table 15. Characteristics of included studies.

Reference	Country, Year	Design	Specialty type	Surgical approach	Perioperative care strategy	No. of Patients POI/No-POI	Definition of POI	Reported rate of POI
Asgeirsson et al.[127]	USA, 2010	Retrospective single-centred	Colorectal	Open & LAP	ERP	45/141	Clinical	24.2%
Gan et al.[27]	USA, 2015	Retrospective multi-centred	Colorectal & general surgery	Open & LAP	Not stated	14,221/123,847	ICD-9 Code	Open colectomy – 20.6% LAP colectomy – 14.6% Open cholecystectomy – 11.6% LAP cholecystectomy – 3.2%
Goldstein et al.[28]	USA, 2007	Retrospective multi-centred	Gynaecological, colorectal, general surgery	Not stated	Not stated	142,026/1,519,663	ICD-9 Code	Abdominal hysterectomy - 4.1% Large-bowel colectomy - 14.9% Small-bowel resection - 19.2% Appendicectomy - 6.2% Cholecystectomy - 8.5% Nephrectomy - 8.9%
Iyer et al.[29]	USA, 2009	Retrospective multi-centred	Colorectal	Open & LAP	Not stated	3,115/14,761	ICD-9 Code	17.4%
Mao et al.[126]	NZ, 2018	Prospective single-centred	Colorectal	Open & LAP	ERP	88/237	Clinical	27%
Nutt et al.[30]	USA, 2018	Retrospective multi-centred	Urology	Not stated	Not stated	11,155/30,343	ICD-9 Code	26.9%

Peters et al.[125]	Netherlands, 2019	Prospective multi-centred	Colorectal	Open & LAP	ERP	66/199	Clinical	24.9%
Salvador et al.[31]	USA, 2005	Retrospective single-centred	Colorectal & gynaecological	Not stated	Not stated	Hysterectomy: 60/331 Colectomy: 35/141	Clinical and ICD-9 Code	Hysterectomy – 18.2% Hemicolectomy – 24.5%
Traeger et al.[261]	AUS, 2022	Retrospective single-centred	Colorectal	Open & LAP	ERP	145/270	Clinical	34.9%

ERP; Enhanced recovery protocol. ICD; International Classification of Diseases. LAP; laparoscopic. POI; Postoperative ileus.

6.4.3 DEFINITION AND INCIDENCE OF POI

In total, 170,947 (9.2%) patients were diagnosed with POI.[27-31, 125-127, 261] Five studies diagnosed POI based on clinical factors, provided in Table 15 & Appendix D.[31, 125-127, 261] Four studies diagnosed POI based on ICD-9 codes.[27-30] There was heterogeneity in the incidence of POI, 3.2-34.9%, dependent on the type of procedures. In papers reporting colorectal procedures alone the incidence of POI varied from 17.4-34.9%.[29, 125-127, 261]

6.4.4 TOTAL COST

Out of the available studies, eight studies demonstrated a significant increase in total hospital costs attributable to POI.[27-31, 126, 127, 261] The one remaining study did report an increase in total cost[125], however, this did not reach significance. This study was the only study that reported estimates of costs billed, while the other studies reported actual billing costs.[125] Percentage increases ranged from 26.3% to 100.5% in total cost (Table 16).

Table 16. Reported total cost per patient.

Reference	Sub-group	Currency, year, statistic	Costing Data source (Estimate/ actual)	Total cost (per patient)			Total cost (per patient) converted to € 2021 mean (SD)		
				POI	Non-POI	p-value	POI	Non-POI	% Change
Asgeirsson et al.[127]	Colectomy	USD, 2010 Mean (SD)	Hospital accounting system (Actual)	$15,914 (13,756) (n= 45)	$8,316 (4,808) (n= 141)	<0.05	€17,391 (15,033)	€9,088 (5,254)	91.4%
Gan et al.[27]	Cholecystectomy and colectomy	USD, 2008-2010 Median [IQR]	Premier database (Actual)	$21,046 [14,062–35,176] (n= 14,212)	$10,945 [7,489–16,682] (n= 123,847)	<0.0001	€25,733 (17,106)	€12,833 (7,447)	100.5%
	Open colectomy			$24,078 (n= 8,303)	$17,044 (n= 31,947)	N/A	-	-	41.3%
	LAP colectomy			$17,505 (n= 2,577)	$12,521 (n= 15,121)	N/A	-	-	39.8%
	Open cholecystectomy			$20,808 (n= 1,191)	$13,135 (n= 9,035)	N/A	-	-	58.4%
	LAP cholecystectomy			$15,842 (n= 2,218)	$8,529 (n= 67,676)	N/A	-	-	85.7%
Goldstein et al.[28]	Gynaecology, urology, general surgery	USD, 2002 Mean	Premier database (Actual)	$18,877 (n= 142,026)	$9,460 (n= 1,519,663)	N/A			99.6%
Iyer et al.[29]	Colectomy	USD, 2004, Mean (SD)	Premier database (Actual)	$25,089 (35,386) (n= 3,115)	16,907 (29,320) (n= 14,761)	<0.001	€31,650 (44,639)	€21,328 (36,988)	48.4%
Mao et al.[126]	Colorectal surgery	NZD, 2012-2014, Median (IQR)	Hospital accounting system (Actual)	$27,981 (20,198–42,174) (n= 88)	$16,317 (10,620–23,722) (n= 237)	<0.005	€20,977 (11,501)	€11,745 (6,750)	78.8%

Nutt et al.[30]	Radical cystectomy	USD, 2006-2012, Median	US Healthcare Cost and Utilization Project data (Actual)	$32,472 (n= 11,155)	$24,600 (n= 30,343)	<0.001	-	-	32.0%
Peters et al.[125]	Colorectal	Euro, 2019, Mean (95% CI)	IMAT MCQ (Estimate)	€7,549 (4,605-10, 494) (n= 66)	€5,052 (3752-6354) (n= 199)	0.087	€7,760 (12,546)	€5,193 (9,625)	49.4%
Salvador et al.[31]	Hysterectomy	USD, 2001-2002, Mean (median)	Hospital accounting system (Actual)	$12,502 (12,161) (n= 60)	$7,990 (7,375) (n= 331)	N/A	-	-	56.5%
	Colectomy			$28,823 (26,669) (n= 35)	$16,407 (11,765) (n= 141)	N/A	-	-	75.7%
Traeger et al.[261]	Colorectal	AUD, 2018-2021, Mean (SD)	Hospital accounting system (Actual)	$37,690 (21,587) (n= 145)	$29,822 (20,410) (n= 270)	<0.001	€24,093 (13,800)	€19,070 (13,047)	26.3%

IMTA MCQ; Institute for Medical Technology Assessment Medical Consumption Questionnaire. LAP; laparoscopic.

6.4.5 SECONDARY OUTCOMES

Three studies looked at individual departmental costs (Table 17).[126, 127, 261] Asgeirsson et al. found significant increases in hospital costs, pharmacy costs, and laboratory tests.[127] Mao et al. found statistical increases in medical, laboratory, radiological, medication as well as ward and allied health costs.[126] Traeger et al. showed increases in staffing, operating room, pharmacy, supplies, and hospital services costs.[261] Two studies found no difference in radiological costs[127, 261] and two studies found no difference in operating room costs.[127]

Table 17. Departmental costs - total cost (per patient).

Reference	Department	Currency, year, statistic	POI	Non-POI	p-value	% Change
Asgeirsson et al.[127]	Hospital	USD, 2010, Mean (SD)	$7,258 ($4,110)	$3,165 ($2,641)	<0.05	129.3% increase
	Pharmacy		$2,639 ($3,254)	$454 ($1,128)	<0.05	481.3% increase
	Radiology		$153 ($110)	$37 ($116)	-	313.5% increase
	Operating room		$4,823 ($1,261)	$4,260 ($11,222)	-	13.2% increase
	Laboratory tests		$579 ($342)	$252 ($282)	<0.05	129.8% increase
Mao et al.[126]	Medical	NZD, 2014 Median (IQR)	$4,484 ($3,498–$6,641)	$2,583 ($1,870–$3,943)	<0.005	73.6% increase
	Laboratory		$2,688 ($1,319–$3,666)	$1,287 ($401–$2,266)	<0.005	108.9% increase
	Radiology		$687 ($109–$1,534)	$0 ($0–$247)	<0.005	-
	Medication		$735 ($416–$1,745)	$348 ($216–$496)	<0.005	111.2% increase
	Ward and nursing		$8,457 ($5,742–$13,381)	$3,816 ($2,598–$6,573)	<0.005	121.6% increase
	Allied health		$349 ($184–$438)	$229 ($138–$367)	<0.005	52.4% increase
Traeger et al.[261]	Medical staff	AUD, 2021 Mean (SD)	$1,784 ($2,190)	$2,544 ($1,917)	<0.001	42.6% increase
	Nursing staff		$4,365 ($4,232)	$6,105 ($4,014)	<0.001	39.9% increase
	Allied health staff		$217 ($604)	$483 ($1,127)	<0.001	122.5% increase
	Indirect salary costs		$2,546 ($1,991)	$3,279 ($2,226)	<0.001	28.8% increase
	Critical care		$12,921 ($10,673)	$11,656 ($7,831)	0.337	9.8% decrease

	Theatre		$12,759 ($6,099)	$13,781 ($5,694)	0.046	8.0% increase
	Imaging		$803 ($1,117)	$823.21 ($858)	0.452	2.5% increase
	Pathology		$866 ($820)	$977 ($723)	0.096	12.8% increase
	Pharmacy		$326 ($730)	$513.38 ($746)	0.006	57.4% increase
	Supplies		$1,900 ($1,864)	$2,693 ($1,736)	<0.001	41.7% increase
	Hospital services		$951 ($835)	$1,241 ($819)	<0.001	30.4% increase

6.4.6 ASSESSMENT OF RISK OF BIAS

All studies were of good quality when assessed with the Newcastle Ottawa scale. Four studies had a score of 7,[28, 31, 126, 127] four studies had a score of 8[27, 30, 125, 261] and one study had a score of 9.[29] Risk of bias are summarised in Table 18.

Table 18. Newcastle Ottawa quality assessment for included studies.

Reference	Selection	Comparability	Outcomes	Overall
Asgeirsson et al.[127]	****	*	**	7
Gan et al.[27]	***	**	***	8
Goldstein et al.[28]	****		***	7
Iyer et al.[29]	****	**	***	9
Mao et al.[126]	***	*	***	7
Nutt et al.[30]	****	**	**	8
Peters et al.[125]	***	**	***	8
Salvador et al.[31]	****		***	7
Traeger et al.[261]	****	*	***	8

6.4.7 POOLED META-ANALYSIS

Of the identified studies, six could be included in the meta-analysis for the primary endpoint of costs of POI.[27, 29, 125-127, 261] Three studies provided mean and standard deviation.[29, 127, 261] For three studies, mean and standard deviations could be derived from available data.[27, 125, 126] The other three studies were contacted for data availability.[28, 30, 31] Data were not available for one[28], with two studies being unable to be contacted.[30, 31]

Pooled results showed that total hospital costs for patients with POI was €8,233 (95%CI [5,176 -11,290], p<0.0001, I_2=95.5%, Eggers: p=0.0037) higher than those without POI (Table 19 and Figure 9). When comparing percentages, patients with POI had a 66.3% increase of total hospital cost (95%CI [34.8 – 97.9], p<0.0001, I_2=98.4%, Eggers: p=0.1321). The difference in cost demonstrated significant heterogeneity and bias, however the percentage difference was not found to be biased.

Table 19. Summary meta-analysis with values converted to € 2021.

Studies	POI (n)	Mean POI (SD)	Non-POI (n)	Mean Non-POI (SD)	Mean Difference (95%CI)	% Weights (random)	Mean Percentage Difference (95%CI)	% Weights (random)
Asgeirsson et al.[127]	45	€17,391 (15,033)	141	€9,088 (5,254)	€8,303 (5,377 - 11,229)	15.7%	91.4% (59.2 - 123.6)	15.6%
Gan et al.[27]	14,221	€25,733 (17,106)	123,847	€12,833 (7,447)	€12,900 (12,745-13,055)	18.3%	100.5% (99.3 - 101.7)	18.6%
Iyer et al.[29]	3,115	€31,650 (44,639)	14,761	€21,328 (36,988)	€10,322 (8,837 – 11,807)	17.5%	48.4% (41.4 - 55.4)	18.5%
Mao et al.[126]	88	€20,977 (11,501)	237	€11,745 (6,750)	€9,252 (7,213 - 11,291)	16.9%	78.8% (61.4 - 96.1)	17.6%
Peters et al.[125]	66	€7,760 (12,546)	199	€5,193 (9,625)	€2,567 (-348 – 5,482)	15.6%	49.4% (-6.7 - 105.6)	11.7%
Traeger et al.[261]	145	€24,093 (13,800)	270	€19,070 (13,047)	€5,023 (2,328 – 7,718)	16.0%	26.3% (12.2 - 40.5)	18.0%
Pooled					€8,233 (5,176 - 11,290)	100%	66.3% (34.8 – 97.9)	100%

Mean difference
Heterogeneity: Cochran Q=112.29 (df = 5), p<0.0001, I_2 = 95.5% (95%CI=93.3,96.8%)
Z (test)=5.28 p<0.0001
Egger: bias = -4.89 (95%CI=-7.13,-2.65), p=0.0037

Percentage difference
Heterogeneity: Cochran Q=315.50 (df = 5), p<0.0001, I_2=98.4% (95%CI=98.0,98.7%)
Z (test)=4.12, p<0.0001
Egger: bias=-5.97 (95%CI=-14.76,2.81), p=0.1321

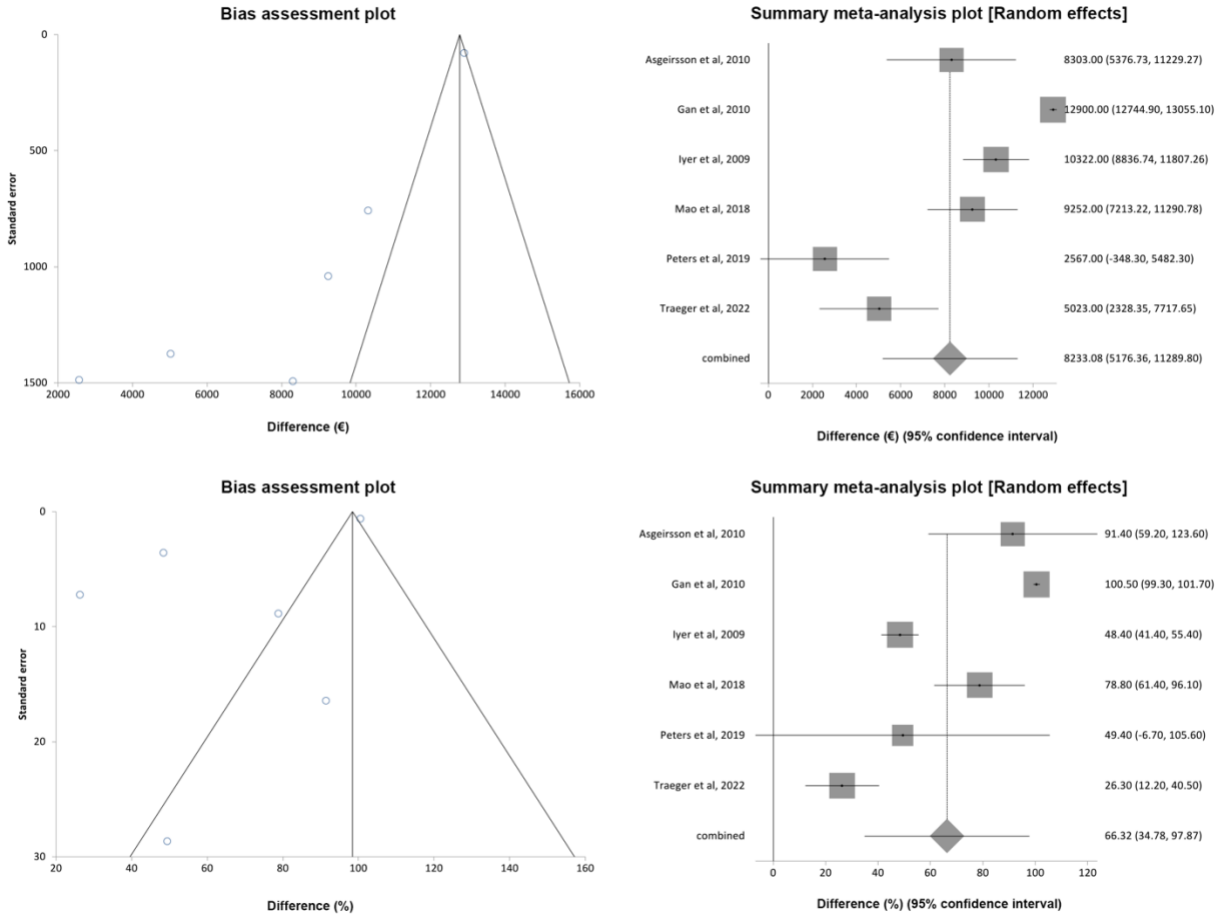

Figure 9. Meta-analysis plots for mean difference (top) and percentage difference (bottom).

Pooled results for colorectal-specific studies showed an increase in total hospital costs for patients with POI of €7,242 (95%CI [4,502 – 9,983], p<0.0001, I_2=86%, Eggers: p=0.08) (Table 20 and Figure 10). When comparing the percentages, patients with POI had a 57.3% increase of total hospital cost compared to those without POI (95%CI [36.3 – 78.3], p<0.0001, I_2=85.7% Eggers: p=0.560). For colorectal-specific studies, the pooled results demonstrate significant heterogeneity, however, were not found to be biased.

Table 20. Summary meta-analysis for colorectal studies with values converted to € 2021.

Studies	n POI	Mean POI(SD)	n Non-POI	Mean Non-POI (SD)	Mean Difference (95%CI)	% Weights (random)	Mean percentage difference (95% CI)	% Weights (random)
Asgeirsson et al.[127]	45	€17,391 (15,033)	141	€9,088 (5,254)	€8,303 (5,377 - 11,229)	18.7%	91.4% (59.2 - 123.6)	16.7%
Iyer et al.[29]	3,115	€31,650 (44,639)	14,761	€21,328 (36,988)	€10,322 (8,837 – 11,807)	22.2%	48.4% (41.4 - 55.4)	26.6%
Mao et al.[126]	88	€20,977 (11,501)	237	€11,745 (6,750)	€9,252 (7,213 - 11,291)	21.1%	78.8% (61.4 - 96.1)	23.1%
Peters et al.[125]	66	€7,760 (12,546)	199	€5,193 (9,625)	€2,567 (-348 – 5,482)	18.7%	49.4% (-6.7 - 105.6)	9.2%
Traeger et al.[261]	145	€24,093 (13,800)	270	€19,070 (13,047)	€5,023 (2,328 – 7,718)	19.3%	26.3% (12.2 - 40.5)	24.4%
Pooled					€7,242 (4,502 – 9,983)	100%	57.3% (36.3 – 78.3)	100%

Mean difference
Heterogeneity: Cochran Q=28.49 (df = 4), p<0.0001, I_2=86.0% (95%CI=64.5,92.2%)
Z (test)=5.18 p<0.0001
Egger: bias=-7.22 (95%CI=-16.05,1.60), p=0.0801

Percentage difference
Heterogeneity: Cochran Q = 27.88 (df = 4), p<0.0001, I_2=85.7% (95%CI=63.3,92.1%)
Z (test)=5.35, p<0.0001
Egger: bias=1.48 (95%CI=-5.73,8.69), p=0.5601

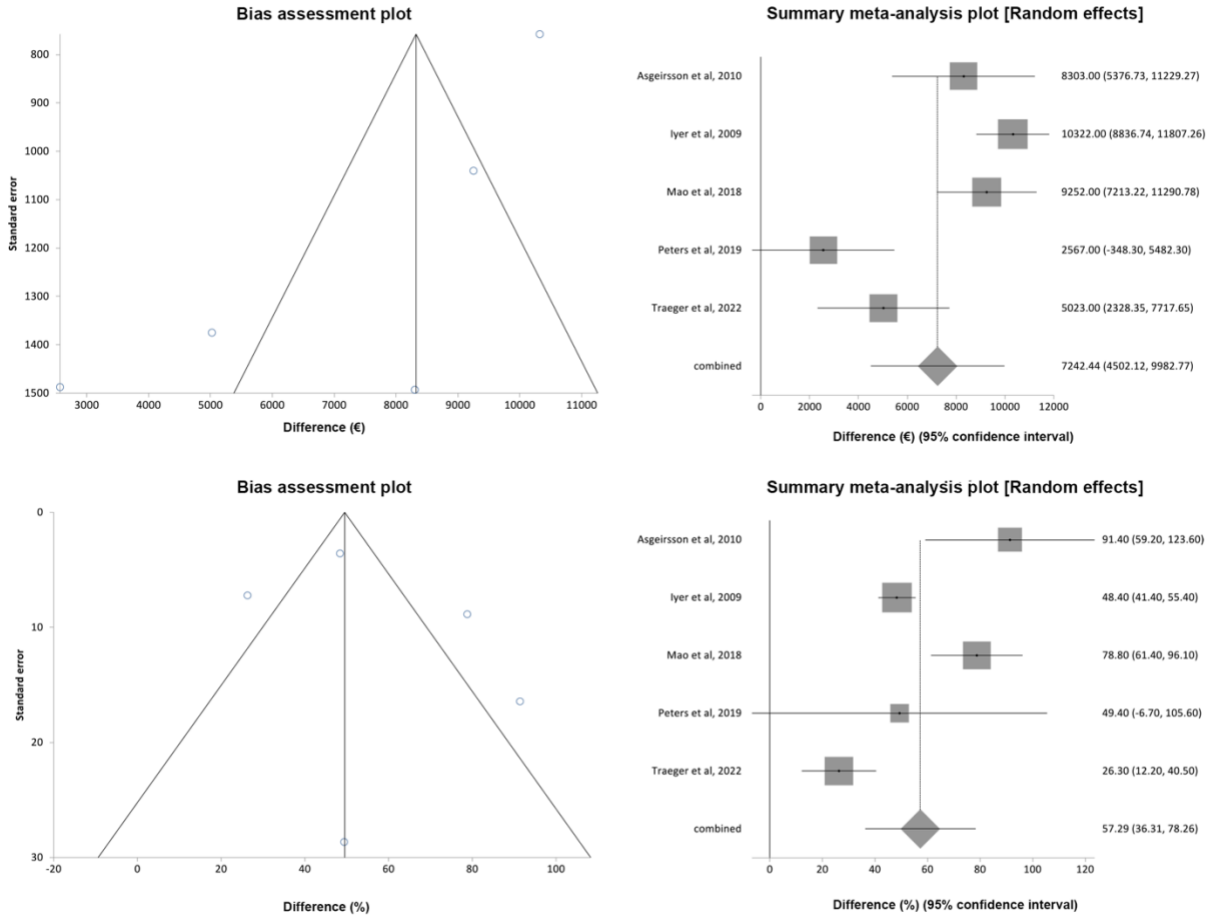

Figure 10. Meta-analysis plots for mean difference (top) and percentage difference (bottom) for colorectal studies.

6.5 DISCUSSION

In this first systematic review of the global financial impact of POI on hospitals, nine studies were identified and eligible for inclusion. The meta-analyses, in which six studies could be included, showed that total hospital costs increased by approximately €8,233 or 66.3% per patient with POI. However, there was significant heterogeneity bias between studies.[27, 29, 125-127, 261]

Defining POI remains contentious. In a systematic review, Vather et al. highlighted the range of different definitions commonly used for POI.[4] Consequently, this variety of definitions has implications on the reported POI incidence rates and subsequently on the total hospital costs attributed to POI. To overcome this, the ICD-9 diagnostic codes can be used rather than the clinical signs and symptoms to diagnose POI. However, studies using ICD-9 codes have reported significantly lower incidence rates of POI, leading to an underestimation of the true POI rate and its associated financial burden.[27-29, 127] This was shown clearly in a prospective study in 203 patients, comparing administrative use of ICD-9 codes against a clinical definition of POI, demonstrating that 35% of the patients were not coded appropriately.[32] This highlighted that clinicians significantly underestimated the incidence of POI as a complication and represented a missed opportunity for reimbursement of approximately US$7,400 per patient. Extrapolating these data, Cromwell et al. estimated that underreporting of POI represents an annual missed opportunity for reimbursement of US$100 million.[32] This decreases the reliability of studies defining POI using the ICD-9 method.

The global prevalence of POI is unclear. To estimate the impact of POI in the US, Solanki et al. using ICD codes found 470,110 patients in the US were hospitalised with POI in 2011.[295] Using our findings, this would represent an increase in total hospital cost by €3.9

billion secondary to POI. This likely represents an underestimate given the inaccuracy of coding data, and the true global value of POI is significantly higher.

Intra-abdominal surgery in particular carries a high risk of POI as a complication. Highlighted by this study is the breadth of surgeries affected, with information provided on costs of POI following general, colorectal, gynaecological, and urological surgery. Colorectal surgery carries the highest risk of POI due to specific factors such as handling of the bowel, splenic flexure mobilisation, stoma formation, open approach and rectal resections.[63, 101, 102] In previous studies looking at colorectal procedures, the incidence of POI was reported as 17.4-34.9%.[29, 125-127, 261] When looking at colorectal-specific studies, POI increased total hospital cost by €7,242 per patient, and an increase of total hospital costs by 57.3% per patient.

Due to the range of POI definitions used and variation in the collection of costing data, meaningful comparisons between specialties and procedures remains challenging. The present study highlights this heterogeneity between studies. This is likely not only the result of variations between surgical specialities and methods of defining POI, but also due to the differences in how healthcare is funded throughout the globe. Of the nine studies included, five were single-centred studies, thus reducing the generalisability. To enhance the analysis and reduce the impact of global differences on the overall total hospital costs, the pooled percentage differences showed a 66.3% increase in total hospital costs. The significance of this increase in total hospital cost, highlights the financial burden of POI on the healthcare system globally. Efforts aimed at reducing POI could not only improve patient safety, but also allow the reallocation of these funds to other aspects of healthcare.

The current review identified three studies investigating the breakdown of total hospital costs.[126, 127, 261] These studies highlighted that total hospital costs were primarily attributable to ward staffing, pharmacy, and laboratory costs. The increase in these departmental costs is largely due to the prolonged length of hospital stay. In Australia, complications during admission have accounted for 15.7% of hospital expenditure.[7] Targeted interventions to reduce the incidence of POI after abdominal surgery, or the impact of this on patients, could significantly reduce this financial burden. Preventing POI, for instance, could remove direct impediments to the recovery of patient autonomy, as well as reduce delayed discharges by 33%, readmissions by 20% and mortality by 20%.[9, 12]

To reduce the morbidity and associated financial burden of POI, the included papers provide several suggested strategies. Although considered the mainstay of postoperative care, five studies suggested that ERPs target the risk factors for POI by improving postoperative fluid management, nutrition and reducing opioid consumption.[27, 30, 125-127] Despite this, only four of the nine included studies specified they routinely used an ERP.[125-127, 261] To reduce the effects of opioid use, peripherally acting μ-opioid receptor antagonist such as alvimopan and methylnaltrexone were also discussed as potential treatments to reduce the incidence POI.[28, 31, 126] Three research groups associated with the papers included in this review, investigated alvimopan and methylnaltrexone to improve gastrointestinal recovery postoperatively with varied success.[171, 177, 296] However, the current evidence for the use of alvimopan as part of an ERP is low-moderate, and use is supported mainly in open abdominal surgery.[175]

Several alternative therapies were also suggested in the reviewed papers. Peters et al. highlighted that POI was associated with systematic inflammatory response and the authors of this paper trialled vagal nerve activation, nutritional interventions and chewing

gum in clinical trials to reduce POI.[125, 297, 298] Gastrografin and prucalopride were also used in clinical trials to treat and prevent POI, following the cost of POI being investigated.[147, 184] In our own experience we are performing a RCT using pyridostigmine, an acetylcholinesterase inhibitor, to modulate the cholinergic anti-inflammatory pathways that is key in the development of POI.[249] The results of this double blinded RCT are forthcoming.

This meta-analysis has some limitations. In this study we did not include papers that explored the cost due to the patient being readmitted to hospital with delayed POI. Secondly, this study highlights that due to a variety of surgical specialties involved, there was significant heterogeneity in data, which must be considered when interpreting the findings of this analysis. This is likely compounded by differences in healthcare systems between countries. To overcome this limitation, a colorectal-specific analysis was performed, investigating the percentage increase in total hospital costs in addition to the absolute cost. Moreover, in several of these studies it is unclear if the cost increase is attributable to POI alone and the contribution of other complications to this cost.

6.6 CONCLUSION

The global financial burden of POI following abdominal surgery is significant. While further multicentre data using a uniform POI definition would be useful, it is clear from these data that the costs associated with POI are globally significant. Efforts aimed at reducing the incidence of POI with ERPs and investigating adjunctive therapies such as pyridostigmine are a priority to reduce healthcare-related costs, and improve patient experience and outcome.

CHAPTER 7: PYRICO-RCT – PYRIDOSTIGMINE TO REDUCE THE DURATION OF POSTOPERATIVE ILEUS AFTER COLORECTAL SURGERY – A DOUBLE BLINDED RANDOMISED CONTROLLED TRIAL.

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Title of Paper	Pyridostigmine to reduce the duration of postoperative ileus after colorectal surgery – a double blinded randomised controlled trial (PyRICo-RCT)
Publication Status	Submitted for Publication
Publication Details	Traeger L, Bedrikovetski S, Fitzsimmons T, Nguyen TM, Moore JW, Lewis M, Sammour T. Pyridostigmine to reduce the duration of postoperative ileus after colorectal surgery – a double blinded randomised controlled trial (PyRICo-RCT).

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Contribution to the Paper	Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/10/2023

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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I observed several limitations after thoroughly examining the current evidence regarding the use of ACIs as a preventative measure for POI. The current evidence is limited, biased, and lacks studies following colorectal surgery or incorporating modern ERPs. Additionally, our research highlighted that although ACIs used in neuromuscular reversal impact time to first stool, they do not significantly affect the development of POI. Furthermore, our studies show the significant financial implications of POI. Considering this, I performed the first double blinded RCT evaluating pyridostigmine as a potential strategy to improve GI recovery postoperatively.

7.1 ABSTRACT

Objective: To assess the efficacy of pyridostigmine in improving gastrointestinal recovery after colorectal surgery.

Background: Postoperative ileus (POI), driven by the cholinergic anti-inflammatory pathway (CAIP), is the most common complication in colorectal surgical patients. By inhibiting acetylcholinesterase, pyridostigmine can potentially modulate the CAIP and accelerate gastrointestinal recovery.

Methods: A double blinded randomised controlled trial (RCT) was conducted with adult patients undergoing elective colorectal surgery at two hospitals in South Australia. Patients were randomised to oral pyridostigmine 60mg or placebo twice daily starting 6 hours post-surgery until the first passage of stool. The primary outcome was GI-2, a validated composite measure of time to first stool and tolerance of oral diet. Secondary outcomes included incidence of POI (defined as GI-2 >4 days), length of hospital stay, and 30-day complications.

Results: Of 130 patients recruited (mean [SD] age, 58.4 [16.4] years; 73 [56%] male), 65 were allocated to each study arm. The median GI-2 was one day shorter with pyridostigmine compared to the placebo (2 (IQR 1-3) vs. 3 (2-4); p=0.02). However, there were no significant differences in POI (17.2% vs. 21.5%, p=0.53), length of hospital stay (median 5 (IQR 3.25-8) vs. 5 (4-7.5) days, p=0.71), or complications. No patients were lost to 30-day follow-up. Importantly, there were no significant differences in anastomotic leak, cardiac complications, or patient-reported side effects.

Conclusions: Pyridostigmine improved the return of gastrointestinal function and was well-tolerated. Larger multi-centred RCTs are required to determine pyridostigmine's optimal dosing regimen and evaluate its impact in different surgical settings.

7.2 INTRODUCTION

Modern enhanced recovery protocols (ERPs) prescribe strategies to improve recovery following colorectal surgery, targeting tolerance of diet, independent mobility and restoration of gastrointestinal (GI) function.[1, 9, 128] Despite the significant reduction in complications and vast improvements in recovery, postoperative ileus (POI) remains a formidable complication affecting approximately 10-30% of patients.[17, 100, 281] POI significantly delays recovery, causes patient discomfort, hinders nutrition, and increases the risk of complications, leading to extended hospital stay and higher healthcare costs.[9, 12, 260, 261]

Current strategies used as part of ERPs, such as opioid avoidance, laxatives, early feeding, and mobilisation, have limited impact on POI partly due to its complex pathophysiology via inflammatory, neurogenic, and vagal mechanisms.[146, 151, 153, 166, 235, 250] Autonomic dysfunction, specifically related to the cholinergic anti-inflammatory pathway (CAIP), has been implicated in developing POI.[45, 146, 148, 151] Preventing or treating POI by utilising agents which target this autonomically mediated system, such as acetylcholinesterase inhibitors (ACIs), lacks robust evidence.

We hypothesise that administering oral pyridostigmine, an ACI, to patients postoperatively within an optimised ERP setting will improve GI recovery. While ACIs have been used successfully in treating other GI conditions such as acute colonic pseudo-obstruction (ACPO), their role in preventing or treating POI remains unclear.[249, 266] ACIs enhance GI motility by increasing acetylcholine availability at neuromuscular synapses.[249, 266] Subsequently, the CAIP and postoperative macrophage activation, which occurs within a few hours of surgery, may be downregulated by acetylcholine and provides an additional mechanism towards the restoration of GI function. [24, 45, 253] ACIs have been evaluated in

several randomised controlled trials (RCTs) and demonstrated improvements in the return of GI function following abdominal surgery.[196, 247, 248, 258, 259] Only one trial has used oral pyridostigmine in non-colorectal surgery, showing a one-day reduction in time to first flatus and stool and no adverse events related to pyridostigmine use.[248] However, the evidence for ACI use in modern ERPs and notably colorectal surgery, where POI is most prevalent, is lacking.[266]

This RCT builds on the safety demonstrated in a pilot study of oral pyridostigmine in colorectal surgery.[249] Hence, we conducted a double blinded RCT to assess postoperative pyridostigmine's efficacy to improve GI recovery following colorectal surgery.

7.3 METHODS

7.3.1 TRIAL DESIGN

This trial follows the CONSORT checklist (Appendix E) and is a stage 3 (IDEAL Framework[299]) double blinded randomised controlled trial conducted at the Royal Adelaide Hospital (RAH) and St Andrew's Hospital (SAH). The RAH is an 800-bed teaching hospital with a tertiary colorectal surgical unit in Adelaide, South Australia, Australia. SAH is a private 250-bed hospital, with trial participants operated on and managed by colorectal surgeons from the RAH colorectal unit. The RCT was approved by the Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee (HREC) (2021/HRE00071) and SAH HREC #136. The protocol was prospectively registered with anzctr.org.au (ACTRN12621000530820). The trial was conducted conforming to the ethical principles of the Declaration of Helsinki and the principles of Good Clinical Practice (ICH-GCPE6).[300] All participants provided written informed consent.

7.3.2 PARTICIPANTS

Patients were identified from elective theatre lists and eligible to participate if they were ≥18 years old, undergoing elective large or small bowel resection, stoma formation, or reversal. This broad inclusion criteria were established to ensure the representation of the colorectal unit's workload as comprehensively as possible. Patients were excluded if they were pregnant, had an American Society of Anaesthesiologists (ASA) score ≥4, expected to have residual active inflammatory bowel disease after surgery or had active disease affecting bowel transit (e.g., hypothyroidism and slow transit syndromes). Patients with conditions potentially worsened by pyridostigmine use, including prolonged QT syndrome, epilepsy, Parkinson's disease, previous ischemic heart disease or arrhythmia, asthma requiring regular medication, active peptic ulcer disease, moderate to severe renal impairment with a creatinine clearance of <30 ml/min, as well as previous adverse reactions to pyridostigmine or regularly prescribed anticholinergic medications were not permitted to participate in the study. Patients unable to provide consent or participate due to dementia, cognitive impairment, or language barrier were also excluded.

7.3.3 RANDOMISATION AND BLINDING

Using block randomisation, patients were assigned (1:1) in groups of six to the intervention or placebo groups. Participants, investigators, and hospital staff were blinded to the group assignment. Blinding was performed by an independent research officer using sealedenvelope.com and provided to the hospital's pharmacy, which provided labelled medication bottles with participant numbers. To ensure safety, a sealed, unblinding envelope accompanied the trial medication. Adverse events were reported to the medication safety committee (consisting of a surgeon, anaesthetist, and pharmacist) during the trial. No breaches of blinding occurred during the study.

7.3.4 INTERVENTION

Both groups received standard care, with the addition of one capsule twice daily, commencing six hours postoperatively, until the first bowel action. The control group received a micro cellulose placebo, while the intervention arm (PyRICo) received pyridostigmine 60 mg (Mestinon, iNova Pharmaceuticals, Australia). Intervention and placebo were concealed in identical capsules and a dissolution test ensured pharmacokinetics were not impacted by concealment (Appendix E) The intervention was discontinued if a patient reached postoperative day five without opening bowels or if a nasogastric (NG) tube was inserted. All patients followed an ERP protocol, (includes regular laxative use postoperatively) and can be found at www.tinyurl.com/raheras. This includes a safe discharge criterion, which ward staff are instructed to follow.

7.3.5 OUTCOMES

The primary outcome was GI recovery measured using GI-2, a validated outcome measure comprised of time to first stool and tolerance of solid diet without significant nausea or vomiting.[25] Secondary outcomes included POI, defined as not achieving GI-2 by day four postoperatively, as well as time to first stool, time to first flatus, time to tolerance of oral diet, and NG tube insertion for both groups. Secondary outcomes also included length of hospital stay, trial-specific patient-reported outcome survey and direct hospital costs. Thirty-day complications, Clavien-Dindo (CD) grades, comprehensive complication index (CCI®) score, return to theatre, and readmission rates were also collected.[273, 301] Follow-up was conducted via outpatient appointment or contact via telephone.

Data collection for the trial was performed by two authors (LT and TMN), using medical records and patient reported bowel function every 12 hours. Baseline demographics including age, body mass index (BMI), smoking history, congestive cardiac failure (CCF), chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus, regular

steroid use or previous abdominal surgery history were recorded. Preoperative haemoglobin and albumin were measured and the choice of neuromuscular reversal agent by the anaesthetist (neostigmine/glycopyrrolate or sugammadex) was noted. Operative data included the diagnosis, surgical approach (open/laparoscopic), laparoscopic to open conversion, procedure type, stoma formation and duration of surgery. Stoma type included ileostomy, colostomy or double-barrelled uro-colostomy (as described in previous work).[302] Postoperative data included opioid requirements in morphine equivalents calculated using Opioid Calculator v2.9.1 (Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists, Australia). CCI was scored using an online calculator (available at https://www.assessurgery.com/about_cci-calculator/). Study-specific patient-reported outcome measures were obtained immediately before discharge for patients who received capsules.The primary outcome was gastrointestinal recovery measured using GI-2, a validated outcome measure comprised of time to first stool and tolerance of solid diet without significant nausea or vomiting.[25] Secondary outcomes included prolonged POI, defined as not achieving GI-2 by day 4 postoperatively, as well as time to first stool, time to first flatus, time to tolerance of oral diet, and NG tube reinsertion for both groups. Secondary outcomes also included length of hospital stay, trial-specific patient reported outcome survey and direct hospital costs. Thirty-day complications, Clavien-Dindo (CD) grades, comprehensive complication index (CCI®) score, return to theatre, and readmission rates were also collected.[273, 301] Follow-up was conducted via outpatient appointment or contact via telephone.

Data collection for the trial was performed by two authors (LT and TMN), using medical records and twice-daily patient reviews. The choice of neuromuscular reversal agent by the anaesthetist (neostigmine/glycopyrrolate or sugammadex) was collected. Baseline demographics such as age, body mass index (BMI), smoking history, congestive cardiac

failure (CCF), chronic obstructive pulmonary disease (COPD), hypertension, diabetes mellitus, regular steroid use or previous abdominal surgery history were documented. Preoperative haemoglobin, and albumin were taken. Operative data included the diagnosis, surgical approach (open/laparoscopic), laparoscopic to open conversion, procedure type, stoma formation and duration of surgery. Stoma type included ileostomy, colostomy or double barrelled urocolostomy (as described in previous work).[302] Postoperative data included opioid requirements in morphine equivalents was calculated using Opioid Calculator v2.9.1 (Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists, Australia). CCI was calculated online (available at https://www.assessurgery.com/about_cci-calculator/). Study specific patient reported outcome measures were taken immediately prior to discharge for patients who received any capsules.

7.3.6 STATISTICAL ANALYSIS

An a priori power calculation was performed using the best available GI-2 data from the STIMULAX trial (2 days SD 1.85).[235] We anticipated a 1-day reduction in GI-2. A sample size of fifty-five patients per arm was determined using a two-tailed independent-samples *t*-test for the difference between two unpaired means (alpha-error 0.05, beta-error 0.2, power 0.8, effect 0.54) and a 1:1 allocation. To account for potential attrition, withdrawals, and protocol violations, 130 patients were recruited to the study.

Statistical analyses were conducted according to a statistical analysis plan by an external clinical trials team statistician at the South Australian Health and Medical Research Institute (SAHMRI) blinded to the group allocation on an intention-to-treat basis (Appendix E). The Kolmogorov–Smirnov test was used to identify the distribution of data and normally distributed data were expressed as mean ± standard deviation (SD) and non-

parametric data using median (interquartile range). Univariate analysis was reported using Chi-squared ($\chi 2$) test, Mann-Whitney U test for nonparametric data and independent *t*-test for continuous variables. A Kaplan-Meier curve was generated for the primary outcome. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 28.0 (SPSS Inc., Armonk, NY, USA).

7.4 RESULTS

7.4.1 PARTICIPANT RECRUITMENT

Patient recruitment is presented in the Consort diagram (Figure 11). A total of 236 patients were screened for inclusion between 7 October 2021 and 29 March 2023. Following exclusions, 130 patients were randomised equally between the PyRICo and control groups. Of the 130 randomised, one patient in the PyRICo arm was excluded before receiving the allocated trial drug due to haemodynamic instability postoperatively. In each arm, 9 patients had the intervention discontinued early. No patients were lost to follow-up. Baseline characteristics are reported in Table 21.

Table 21. Baseline characteristics for trial population.

	Control (n=65)	PyRICo (n=64)
Demographics		
Age, years	58.18 (±17.25)	58.58 (±15.70)
Gender		
Female	30 (46.2)	26 (40.6)
Male	35 (53.8)	38 (59.4)
ASA		
1	5 (7.7)	3 (4.7)
2	28 (43.1)	28 (43.8)
3	32 (49.2)	33 (51.6)
Smoking history		
Active smoker	12 (18.5)	12 (18.8)
Ex-smoker	15 (23.1)	22 (34.4)
BMI, kg/m^2	26.4 (23.8-31.3[18.4-53.1])	27.5 (23.6-31.6[18.4-49.5])
Congestive cardiac failure	0 (0.0)	0 (0.0)
Chronic obstructive pulmonary disease	2 (3.1)	5 (7.8)
Hypertension requiring medication	23 (35.4)	19 (29.7)
Diabetes mellitus	8 (12.3)	8 (12.5)
Regular steroid use	2 (3.1)	3 (4.7)
Preoperative haemoglobin, g/L	132.9 (±21.8)	129.7 (±18.9)
Preoperative albumin, g/L	36 (34-40[20-45])	35 (32-40[19-45])
Previous abdominal surgery	41 (63.1)	41 (64.1)
Malignancy	34 (52.3)	32 (50.0)
Malignancy side		
Right	15 (44.1)	13 (40.6)
Left	19 (55.9)	19 (59.4)
Operative Characteristics		
Surgical approach		
Open	27 (41.5)	32 (50.0)
Laparoscopic	38 (58.5)	32 (50.0)
Conversion from laparoscopic	5 (13.2)	3 (9.4)
Primary operation		
Anterior resection	18 (27.7)	11 (17.2)
APR/Hartmann's procedure	6 (9.2)	2 (3.1)
Pelvic exenteration	1 (1.5)	5 (7.8)
Right colectomy	17 (26.2)	14 (21.9)
Formation of stoma	3 (4.6)	5 (7.8)
Reversal of ileostomy	8 (12.3)	9 (14.1)
Reversal of Hartmann's procedure	8 (12.3)	5 (7.8)
Pan/Proctocolectomy	0 (0.0)	6 (9.4)
Sub/Total Colectomy	3 (4.6)	7 (10.9)
Small bowel resection	1 (1.5)	0 (0.0)
Stoma performed	17 (26.2)	27 (42.2)
Stoma type		
Ileostomy	7 (41.2)	17 (63.0)
Colostomy	9 (52.9)	8 (29.6)
Double-barrelled uro-colostomy	1 (5.9)	2 (7.4)
Epidural/Spinal	13 (20.0)	22 (34.4)
Neostigmine/Glycopyrrolate	30 (46.2)	27 (42.2)
Intraoperative/Recovery opioids, MEQ	110 (86-162[24-330])	130 (91.3-174.4[45-532])

Total duration of operation, min	180 (133-242.5[60-660])	194.5 (143.3-272.5[80-840])
TAP Catheter/Block	41 (63.1)	36 (56.3)
Intraoperative complications	4 (6.2)	10 (15.6)
Intraoperative intravenous fluids used, ml	2000 (1000-2300[100-6000])	2000 (1000-2212.5[200-6000])
Recovery intravenous fluids used, ml	1000 (525-1175[0-2700])	1000 (300-1375[0-3400])
Patient controlled analgesia	25 (38.5)	35 (54.7)

Values presented as median (IQR[Range]) or n (%)
APR, Abdominoperineal Resection. ASA, American Society of Anaesthesiologist Physical Status Classification. BMI, Body Mass Index. MEQ, Morphine Equivalents. TAP, Transversus Abdominis Plane.

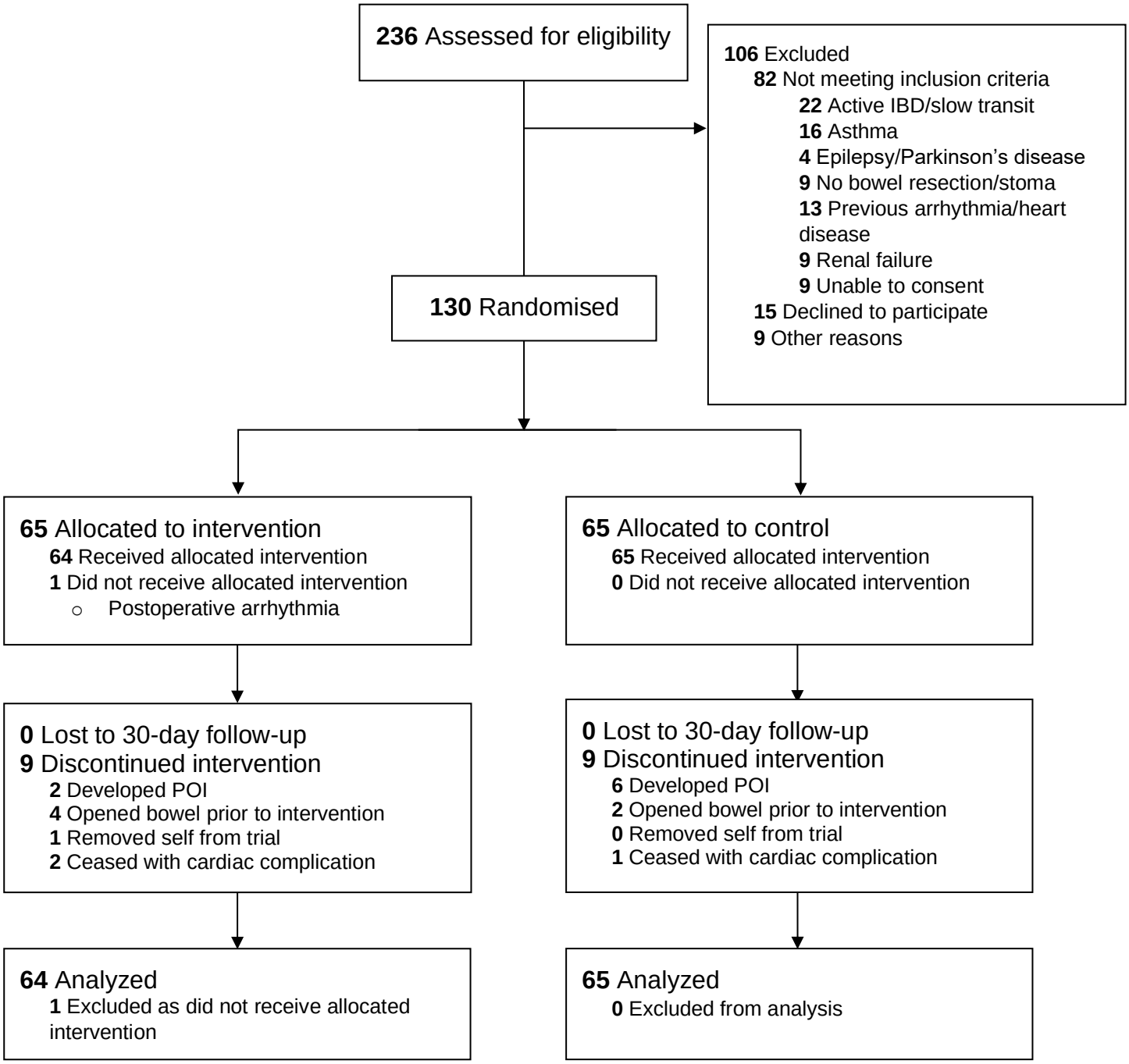

Figure 11. CONSORT Diagram

7.4.2 PRIMARY OUTCOME

The primary outcome is presented in Table 22. GI-2 was reduced by one day (median 2 [IQR 1-3] vs 3 [2-4] days, p=0.015) in the PyRICo arm compared to the control. The primary outcome is graphically presented on the Kaplan-Meier curve (Figure 12), with the most significant differences seen on day one (41% vs 17%) and day two (67% vs 48%) (p=0.015).

Table 22. Gastrointestinal recovery in PyRICo and control groups.

	Control (n=65)	PyRICo (n=64)	P value
Primary outcome			
GI-2, days	3 (2-4[1-9])	2 (1-3[1-12])	0.015
Secondary outcomes			
POI	14 (21.5)	11 (17.2)	0.532
First flatus, days	2 (1-2[0-7])	1 (1-2[0-8])	0.024
First stool, days	2 (2-3.5[0-8])	2 (1-3[0-8])	0.003
Bristol stool type			0.175
1	0 (0.0)	0 (0.0)	
2	3 (4.6)	0 (0.0)	
3	3 (4.6)	1 (1.6)	
4	8 (12.3)	4 (6.3)	
5	10 (15.4)	6 (9.4)	
6	5 (7.7)	6 (9.4)	
7	36 (55.4)	47 (73.4)	
Tolerance of oral diet, days	1 (1-2[0-9])	1 (1-1[0-12])	0.271
TPN required	1 (1.5)	3 (4.7)	0.302
NGT insertion	11 (16.9)	16 (25.0)	0.260
Duration of NGT required days	3 (3-4[1-8])	4 (3-5[1-9])	0.403
Nausea	28 (43.1)	30 (46.9)	0.665
Vomiting	21 (32.3)	30 (46.9)	0.091

Values presented as median (IQR[Range]) or n (%)
NGT, Nasogastric tube. POI, Postoperative Ileus. TPN, Total Parenteral Nutrition.

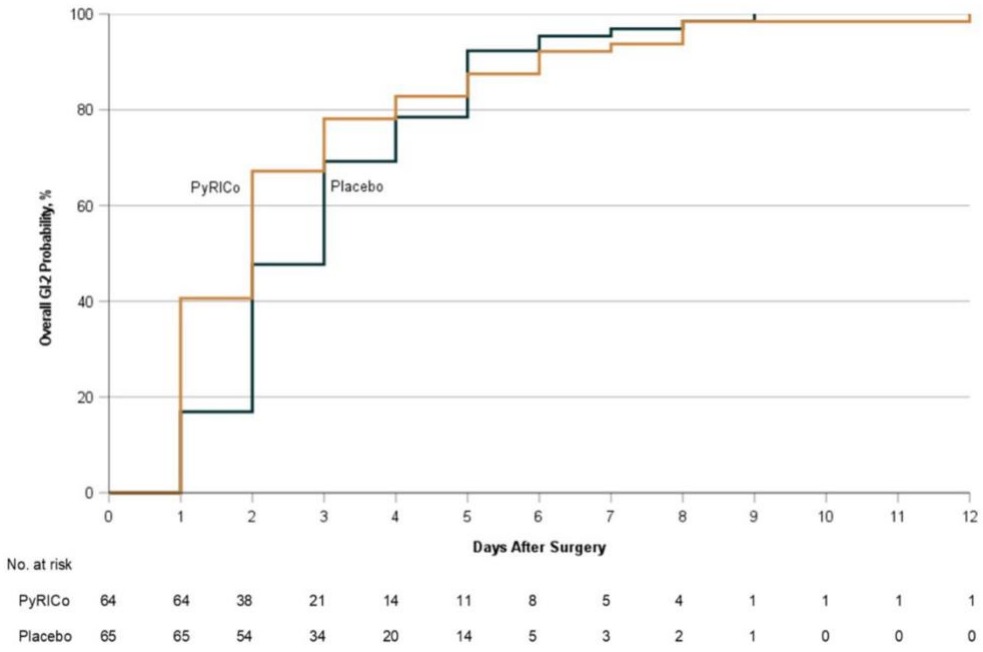

Figure 12. Kaplan Meier curve of GI-2 (Breslow test p=0.015)

7.4.3 SECONDARY OUTCOMES

There was a significant reduction in time to first flatus (median 1 [IQR 1-2] vs. 2 [IQR 1-2], p=0.024) and first stool (median 2 [IQR 1-3] vs. 2 [IQR 2-3.5], p=0.003). There were no differences noted in tolerance of oral diet and POI rates. No differences were detected in nausea, vomiting, NGT insertion and Total Parenteral Nutrition (TPN) requirement rates. Findings are reported in Table 22.

When examining postoperative outcomes (Table 23), no differences were noted in postoperative opioid use and pain scores. Length of stay was the same between the two groups (median 5 [IQR 4-8.75] vs. 5 [4-7.5] days, p=0.921). No differences were noted in the rate of complications, CD grade of complications or CCI score between the two groups. Of note, 79.8% of patients were on telemetry (via Advanced Recovery Room Care (ARRC)/Cardiac Care Unit (CCU) admission), and there was no increase in cardiac complications. Anastomotic leak was higher in the intervention cohort however this did not reach significance (5.8 vs. 1.6%, p=0.332). No difference was found in specific complications.

Table 23. Postoperative outcomes in PyRICo and control groups.

	Control (n=65)	PyRICo (n=64)	P value
Postoperative opioid use (POD 1-4), MEQ	153 (60-361.5[0-2314])	162.5 (11.25-324.25[0-1886])	0.727
Pain scores			
Daily average pain score at rest (POD 1-4)	2.04 (±1.27)	2.06 (±1.28)	0.946
Daily average pain score on activity (POD 1-4)	2.82 (±1.46)	3.17 (±1.61)	0.200
Maximum pain score (POD 1-4)	7 (5.5-8[0-10])	7 (6-8[2-10])	0.826
Lowest postoperative potassium, mmol	3.7 (±0.4)	3.7 (±0.4)	0.341
ARRC/CCU admission	49 (75.4)	54 (84.4)	0.203
Unplanned intensive care unit admission	0 (0.0)	3 (4.7)	0.119
Return to theatre	2 (3.1)	3 (4.7)	0.680
30-day readmission	5 (7.7)	8 (12.5)	0.364
Length of stay, days	5 (4-7.5[2-22])	5 (4-8.75[2-37])	0.921
Any complication	44 (67.7)	40 (62.5)	0.536
CD Grade			0.583
0	21 (32.3)	24 (37.5)	
1	15 (23.1)	10 (15.6)	
2	25 (38.5)	23 (35.9)	
3	4 (6.2)	5 (7.8)	
4	0 (0.0)	2 (3.1)	
5	0 (0.0)	0 (0.0)	
CCI	12.2 (0-22.6[0-51.8])	10.5 (0-30.5[0-62.2])	0.870
Specific complications			
Acute Kidney Injury	2 (3.1)	3 (4.7)	0.680
Anastomotic leak			0.332
Yes	1 (1.6)	3 (5.8)	
No	60 (98.4)	49 (94.2)	
Bleeding requiring transfusion	5 (7.7)	6 (9.4)	0.732
Cardiac	3 (4.6)	3 (4.7)	>0.999
Diarrhea/HOS	10 (15.4)	12 (18.8)	0.611
Electrolytes	25 (38.5)	21 (32.8)	0.503
Hypotension	1 (1.5)	4 (6.3)	0.208
Neurological	1 (1.5)	3 (4.7)	0.365
Other infection	7 (10.8)	6 (9.4)	0.793
Respiratory	4 (6.2)	7 (10.9)	0.364
SBO/Pseudo obstruction	1 (1.5)	0 (0.0)	>0.999
Transfusion	7 (10.8)	8 (12.5)	0.759
Urinary retention	1 (1.5)	2 (3.1)	0.619
Venous thromboembolism	2 (3.1)	1 (1.6)	>0.999
Wound infection	10 (15.4)	6 (9.4)	0.301

Values presented as median (IQR[Range]), mean (±standard deviation) or n (%)
ARRC, Advanced Recovery Room Care. CCI, Comprehensive Complications Index. CCU, Coronary Care Unit. CD, Clavien-Dindo. HOS, High Output Stoma. MEQ, Morphine Equivalents. POD, Postoperative Day. SBO, Small Bowel Obstruction.

Patient-reported outcomes were not different between groups (Table 24). Despite not reaching significance, more patients reported side effects in the control cohort than in the PyRICo arm (13.3 vs. 22.6%, p=0.184). Overall, patients were more satisfied/very satisfied in the PyRICo arm (65 vs. 51.6%, p=0.017).

Table 24. Patient reported outcomes.

	Control (n=62)	PyRICo (n=60)	P value
Do you think the tablet assisted with opening your bowels?			0.610
Strongly disagree	2 (3.2)	0 (0.0)	
Disagree	0 (0.0)	0 (0.0)	
Neither agree/disagree	33 (53.2)	33 (55.0)	
Agree	23 (37.1)	21 (35.0)	
Strongly agree	4 (6.5)	6 (10.0)	
How satisfied/unsatisfied are you with the way the medication relieved your constipation?			0.966
Very unsatisfied	1 (1.6)	1 (1.7)	
Unsatisfied	7 (11.3)	5 (8.3)	
Neither unsatisfied nor satisfied	21 (33.9)	23 (38.3)	
Satisfied	27 (43.5)	26 (43.3)	
Very satisfied	6 (9.7)	5 (8.3)	
How satisfied/unsatisfied are you with the amount of time it took for the medication to start working?			0.267
Very unsatisfied	0 (0.0)	1 (1.7)	
Unsatisfied	7 (11.3)	5 (8.3)	
Neither unsatisfied nor satisfied	27 (43.5)	21 (35.0)	
Satisfied	20 (32.3)	29 (48.3)	
Very satisfied	8 (12.9)	4 (6.7)	
Did you experience any side effects?	14 (22.6)	8 (13.3)	0.184
How bothersome were the side effects?			0.156
Very bothersome	1 (7.1)	0 (0.0)	
Bothersome	0 (0.0)	2 (25.0)	
Somewhat bothersome	7 (50.0)	2 (25.0)	
A little bothersome	2 (14.3)	0 (0.0)	
Not at all bothersome	4 (28.6)	4 (50.0)	
Patient reported side effect			
Dry Mouth	5 (8.1)	3 (5.0)	0.717
Diaphoresis	2 (3.2)	2 (3.3)	>0.999
Muscle twitching	1 (1.6)	2 (3.3)	0.616
Reflux	2 (3.2)	0 (0.0)	0.161
Other	0 (0.0)	1 (1.7)	0.492
How easy or difficult is it to use the medication in its current form?			0.945
Very difficult	0 (0.0)	0 (0.0)	
Difficult	1 (1.6)	2 (3.3)	
Neither difficult nor easy	4 (6.5)	3 (5.0)	
Easy	42 (67.7)	42 (70.0)	
Very easy	15 (24.2)	13 (21.7)	
How convenient or inconvenient is it to take the medication as instructed?			0.973
Very inconvenient	0 (0.0)	0 (0.0)	
Inconvenient	1 (1.6)	0 (0.0)	
Neither inconvenient nor convenient	5 (8.1)	6 (10.0)	
Convenient	49 (79.0)	47 (78.3)	
Very convenient	7 (11.3)	7 (11.7)	
Taking all things into account, how satisfied or unsatisfied are you with this medication?			0.017
Very unsatisfied	1 (1.6)	0 (0.0)	
Unsatisfied	5 (8.1)	4 (6.7)	
Neither unsatisfied nor satisfied	24 (38.7)	17 (28.3)	
Satisfied	24 (38.7)	38 (63.3)	
Very satisfied	8 (12.9)	1 (1.7)	

Values presented as n (%)

7.5 DISCUSSION

Our novel double blinded RCT aimed to assess the effectiveness of pyridostigmine in an ERP following colorectal surgery. Compared with the placebo group, patients allocated to the pyridostigmine group had significantly reduced GI recovery time (GI-2). Pyridostigmine was well tolerated by participants and did not increase complications. Pyridostigmine may provide a reasonable treatment option to facilitate GI function recovery in colorectal surgery patients.

To provide a broader context, eight RCTs have explored ACIs to expedite GI recovery after abdominal surgery.[196, 217, 247, 248, 256, 258, 259, 265] Among these studies, five showed a significant reduction in time to return of GI function, with improvements in time to first stool ranging from 17-47.59 hours.[196, 247, 248, 258, 259] However, these studies utilised different dosing regimens, routes of administration, and surgical approaches, leading to variations in results and quality of evidence. Additionally, these studies were conducted over many decades and did not incorporate validated measures of GI recovery, such as GI-2, and did not define POI. We attempted to address all of these issues in the design of the current RCT.

Although our trial demonstrated improved GI recovery, the specific mechanism by which pyridostigmine exerted its influence remains unclear. We hypothesised that pyridostigmine could influence the development of POI through two potential mechanisms: direct stimulation of GI motility and modulation of the secondary inflammatory phase of POI via the CAIP.[249, 266] However, despite a slight decrease in the occurrence of POI (17.2% vs. 21.5%, p=0.532), we did not observe a significant difference, which may be attributed to the sample size and overall low rate of POI. Our historical POI rate was ~30%.[261, 303, 304] The multimodal approach of using laxatives and pyridostigmine together in the intervention

arm may have reduced the overall rate of POI, despite the somewhat higher complexity of operations in this arm of the trial.

Using ACIs routinely as part of an ERP raises concerns regarding cholinergic side effects and safety.[266] Importantly, we did not observe any such increase in complications. ACIs have known cholinergic effects such as hypersalivation and vomiting.[193-196] Specifically, neostigmine carries a risk of serious arrhythmias, contraindicating its use in cardiac conditions. As an analogue of neostigmine with a quarter of its potency, this risk is lower with pyridostigmine.[199] Despite not requiring cardiac monitoring with pyridostigmine use, most patients were monitored with telemetry in CCU and ARRC.[305] Notably, there were three cardiac events in each cohort: two arrhythmias and one cardiac event in the PyRICo arm, and one arrhythmia and two cardiac events in the control arm. These cardiac complications were neither more prevalent nor directly attributed to pyridostigmine usage.

Furthermore, administration of pyridostigmine did not significantly increase the rate of anastomotic leak. Previous studies have offered reassurance that laxatives and prokinetics do not increase the anastomotic leak rate.[166, 235] In our study, the overall rate of anastomotic leaks was low (4 out of 130 patients). The control arm had one patient with a leak that was managed conservatively. In contrast, the PyRICo arm had three anastomotic leaks, two of which warranted a return to the operating room. The potential etiology of these leaks was analysed, and there were several factors noted that were unrelated to pyridostigmine administration (staple misfire, early anticoagulation, and other complex surgical factors). Although postoperative use of prokinetics have not demonstrated an increase in anastomotic leaks, this aspect requires monitoring in future studies.[255] Additionally, the current study and the preceding STIMULAX trial did not identify a significant reduction in the length of hospital stay despite showing an improvement in GI

recovery.[235] This suggests that while GI recovery is essential for patient autonomy, it is not the sole factor influencing discharge[1, 9], and highlights that further work is needed in this area.

We must also acknowledge that ACIs are employed regularly as neuromuscular reversal of anaesthesia, with most colorectal surgical patients receiving neostigmine (~60%) at the conclusion of surgery.[224, 304] We previously investigated the use of neostigmine as part of neuromuscular reversal and found that it delayed time to first stool and GI-2.[304] This delay is likely attributed to the co-administered glycopyrrolate that counteracts the cholinergic effect of neostigmine.[275, 276] The adverse impact on GI recovery cause by neostigmine/glycopyrrolate has also been confirmed as part of a recent meta-analysis.[224] In our trial, around 60% of patients received neostigmine. This presents an opportunity to consider an alternative agent, specifically sugammadex, as the preferred option within an ERP, due to its potential benefits for GI recovery. Further research is needed to explore the use of sugammadex as a routine component of an ERP.

The current RCT has shown a positive reduction in GI-2 with the use of pyridostigmine. Previous trials investigating prucalopride as a method to influence the CAIP have failed to meet their primary endpoint.[147] One potential reason for this could be the difference in onset and duration of action, with prucalopride taking 2 hours to reach peak influence, while pyridostigmine takes only 15 minutes.[147, 188] This difference may alter the effect these agents have on the CAIP. Despite the favourable pharmacokinetics, the optimal dosing for pyridostigmine is unclear. Consistent with previous trials[248], the dose of pyridostigmine 60mg twice daily was well tolerated by the patients in our trial. Notably, more patients in the placebo arm reported cholinergic effects compared to the pyridostigmine group. This indicates that there is the capacity to increase the

pyridostigmine dose to further manipulate the CAIP. There is also an opportunity to change the dose timing, prolong the prophylactic administration, or, as being investigated in a phase II study from the Cleveland Clinic (ClinicalTrial.gov ID: NCT05334485), use pyridostigmine to treat established POI. Our current trial was designed to prevent the development of POI and to stop the medication once the first bowel action occurred to prevent further cholinergic side effects. However, since our findings indicate that the use of pyridostigmine was not associated with poor patient-reported outcomes, consideration could be given to increasing the duration and dose of pyridostigmine in future studies.

This trial has some limitations. Firstly, the trial was powered to detect a significant reduction in GI-2 and was not designed to assess minor differences in complication rates. As discussed above, the question regarding the optimal dosing regimen for pyridostigmine also remains unanswered. Additionally, during the design of this study, the need for more appropriate patient-reported outcome measures for GI recovery became evident. We eagerly await the results of the forthcoming PRO-diGI study (ClinicalTrials.gov ID: NCT05315765), which aims to develop a patient-reported outcome measure for GI recovery. Although every effort is made to adhered to the ERP, compliance was not audited in this study. Lastly, before we can advocate for the routine inclusion of pyridostigmine in ERPs, we must prioritise a multicentre RCT as well as consider the inclusion of other surgical specialties.

7.6 CONCLUSION

Pyridostigmine use as part of an ERP improves GI recovery following colorectal surgery. Pyridostigmine was well tolerated without any risk of increased complications. Larger multicentred RCTs are required to elucidate the mechanisms of pyridostigmine's effects,

determine the optimal dosing regimens, and evaluate its impact in different surgical settings.

CHAPTER 8: MACHINE LEARNING PREDICTION MODEL FOR POSTOPERATIVE ILEUS FOLLOWING COLORECTAL SURGERY

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Statement of Authorship

Title of Paper	Machine learning prediction model for postoperative ileus following colorectal surgery
Publication Status	Submitted for Publication
Publication Details	Traeger L, Bedrikovestki S, Hanna J, Moore JW, Sammour T machine learning prediction model for postoperative ileus following colorectal surgery.

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Name of Principal Author (Candidate)	Luke Traeger		
Contribution to the Paper	Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	20/10/2023

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Based on the findings of our RCT, I shifted focus towards alternative strategies to reduce the burden of POI. Machine learning techniques examine a historical cohort of colorectal surgical patients in this novel study. The aim was to identify potentially modifiable risk factors for developing POI.

8.1 ABSTRACT

Purpose: Postoperative ileus (POI) continues to be a major cause of morbidity following colorectal surgery. Despite best efforts, the incidence of POI in colorectal surgery remains high (~30%). This study aimed to investigate machine learning techniques to identify risk factors for POI in colorectal surgery patients, to help guide further preventative strategies.

Methods: A TRIPOD-guideline-compliant retrospective study was conducted for major colorectal surgery patients at a single tertial care centre (2018-2022). The primary outcome was the occurrence of POI, defined as not achieving GI-2 (outcome measure of time to first stool and tolerance of oral diet) by day four. Multivariate logistic regression, decision trees, radial basis function and multilayer perceptron (MLP) models were trained using a random allocation of patients to training/testing data sets (80/20%). The area under the receiver operating characteristic (AUROC) curves were used to evaluate the performance of models.

Results: Of 504 colorectal surgery patients, 183 (36%) experienced POI. Multivariate logistic regression, decision trees, radial basis function and MLP models returned an AUROC of 0.722, 0.706, 0.712 and 0.800, respectively. In addition to well-known risk factors for POI, such as postoperative hypokalaemia, surgical approach and opioid use, the MLP model identified sarcopenia (ranked 4/30) as a potentially modifiable risk factor for POI.

Conclusion: MLP outperformed other models in predicting POI. Machine learning can provide valuable insights into the importance and ranking of specific predictive variables for POI. Further research into the predictive value of preoperative sarcopenia for POI is required.

8.2 INTRODUCTION

Postoperative ileus (POI) is a serious complication that impairs the recovery of patients following colorectal surgery, occurring in 10-30% of cases.[4, 9] It is characterised by obstipation and intolerance of oral diet due to reduced or uncoordinated intestinal transit postoperatively.[4, 128] POI significantly impacts morbidity and mortality, prolonging the length of stay, and represents a significant financial burden to health care systems.[260, 261] Despite these findings, no method has been proven effective in preventing the occurrence of POI.

Several studies have investigated risk factors for POI, but the variability of definitions for POI has resulted in identified risk factors varying between studies. In a recent meta-analysis, age, male sex, cardiac comorbidities, laparotomies, and formation of stomas have been identified as significant risk factors for POI.[101] However, the current literature is hampered by the diagnosis of POI relying on subjective clinical assessments and imaging studies, which can be time-consuming and prone to inter-observer variability. Additionally, the current statistical methods do not allow for the ranking of variable importance.

Artificial intelligence has the potential to improve the accuracy of POI prediction by analysing large amounts of data and identifying patterns that traditional statistical methods may not identify.[105] Subsets of artificial intelligence, such as machine learning (ML) have improved the accuracy of predictive models in predicting mortality in orthopaedic trauma and complications following laparotomy.[106, 108] A variety of colorectal-specific papers have investigated ML methods; looking at predicting metastasis, response to chemotherapy, postoperative complications and survival.[109, 110] However, to date, limited studies[111, 112], have investigated POI, the most common complication following colorectal surgery.

This study evaluates an ML-based approach to predict the risk of POI following colorectal surgery. Our aim was to develop a predictive model that can accurately identify patients at high risk of POI, allowing the identification of potentially modifiable risk factors to prevent or minimise the impact of POI on patient outcomes.

8.3 METHODS

This is a retrospective study performed at the Royal Adelaide Hospital, a tertiary referral centre in South Australia. We report the findings using the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis(TRIPOD) checklist (Appendix F).[306] A waiver of consent for retrospective patients was given, and this study was approved by the Central Adelaide Local Health Network (CALHN) Human Research Ethics Committee.

8.3.1 PATIENT SELECTION

A retrospective data set included patients admitted for elective colorectal surgery under the Colorectal Unit between January 2018 to September 2022. All patients were operated on or under the supervision of one of six Colorectal Surgical Society of Australia and New Zealand accredited specialist surgeons. Patients were identified through theatre admissions lists. All patients were treated with an enhanced recovery pathway (ERP) (www.tinyurl.com/raheras) postoperatively. Consecutive elective colorectal patients over 18 years old who underwent open or laparoscopic major bowel surgery for large were included. Indications for surgery included malignancy, diverticular disease, inflammatory bowel disease, restoration of bowel continuity and other indications such as polyposis, recurrent volvulus, or stricture. Patients were excluded if they had undergone emergency surgery, received care at a different facility or had non-operative management. Patients were excluded if they were enrolled in the PyRICo-Pilot: pyridostigmine to reduce the

incidence of POI after colorectal surgery - a phase II study or recruited for the follow-up RCT as it was unclear if the addition of pyridostigmine to the ERP affected the primary outcome.[249] Additionally patients undergoing small bowel resections or pelvic exenterations to focus on colorectal-specific conditions and reduce the confounding effect pelvic exenterations have on morbidity. The primary outcome was POI, which was retrospectively defined as not achieving GI-2 by postoperative day four, a threshold suggested by Vather et al.[4] GI-2 is a validated outcome measure comprised of the time to achieve first stool and tolerating a solid diet without significant episodes of nausea or vomiting.[25]

8.3.2 DATA COLLECTION

Electronic medical records were reviewed retrospectively. Thirty known risk factors for the development of POI were collected and established a-priori by two authors (LT and SB).[17, 84, 100, 101] Baseline demographics included age, gender, body mass index (BMI), and American Society of Anaesthesiologists (ASA) score. Patient functional status, history of congestive cardiac failure, chronic obstructive pulmonary disease, diabetes mellitus and hypertension requiring medication were collated. Other nutritional data, including total protein and albumin, were also collected. Patients were not prescribed alvimopan or peripherally acting μ-opioid receptor antagonist preoperatively, as this is not funded in Australia. Operative data included surgical approach (open/laparoscopic), conversion rates, procedure type, stoma formation, duration of surgery, and perioperative intravenous fluid administration. Postoperative data included requirements in morphine equivalents (intraoperative, postoperative recovery and day one to four) calculated using Opioid Calculator v2.9.1 (Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists, Australia). Sarcopenia was diagnosed based on lean muscle mass calculated using the protocol defined by Jones et al. using a CT scan from the

preoperative period or immediately postoperatively, if available.[307] Total psoas area (TPA) was calculated by multiplying the longest anterior-posterior and transverse muscle diameters bilaterally. Measurements were taken at the level of the third lumbar vertebrae using PACS or InteleViewer™ Australia. TPA was normalised for the patient's height squared (TPAmm^2/m^2) to calculate the total psoas area index (TPAI). Sarcopenia was defined using previously validated gender-specific cut-off points: <385 mm^2/m^2 in females and <545 mm^2/m^2 in males.[308]

8.3.3 STATISTICAL METHODS

Statistical analysis was performed using SPSS 28.0 (SPSS Inc., Armonk, NY, USA) and GraphPad Prism version 10.0.0 for Windows. Numerical data are presented as median (IQR [range]) or mean (standard deviation) depending on parametricity identified with the Shapiro-Wilk test. Univariate analysis was performed using the Mann-Whitney U for nonparametric variables or the Student-t test for normally distributed continuous variables. The χ2 or Fisher's exact test for categorical variables, as appropriate. The missing data were pre-processed before regression analysis using the multiple imputations by change equations. Statistical significance was set at *P* value <0.05.

8.3.4 MODEL TRAINING AND EVALUATION

Prior to performing the models, all data was converted from original data to binary data to facilitate model training and evaluation. Clinically relevant cut-off points were selected by the authors prior to conducting the model (Appendix F). Four different models were used: multivariate logistic regression analysis, decision tree, radial basis function (RBF) and multilayer perceptron (MLP). Logistic regression analysis was performed on all 30 collected variables. Statistically significant variables found in the univariate logistic regression analysis were then used in the multivariate analyses to determine predictors of

POI. ML models were run 20 times to determine the optimal model. MLP and RBF neural networks with a custom architecture including automatic hidden layers were performed on all patients, with a random split of 80% training and 20% testing. An independent variable importance analysis was performed and charted. Decision tree analysis was performed on the same training and testing data set, with a three-level architecture, and the testing data set was presented graphically. All models were evaluated using the area under the receiver operator characteristic (ROC) curve with a 95% confidence interval and graphically presented. Secondary analysis of sensitivity, specificity, positive predictive value, negative predictive value, and overall model quality were performed.

8.4 RESULTS

Of 680 patients identified from colorectal elective surgical admission lists, 504 patients were selected for analysis (Figure 13). Missing data were imputed, including a diagnosis of sarcopenia, postoperative opioid use and intravenous fluid use. Of the 504 patients, 183 had a diagnosis of POI (36.3%).

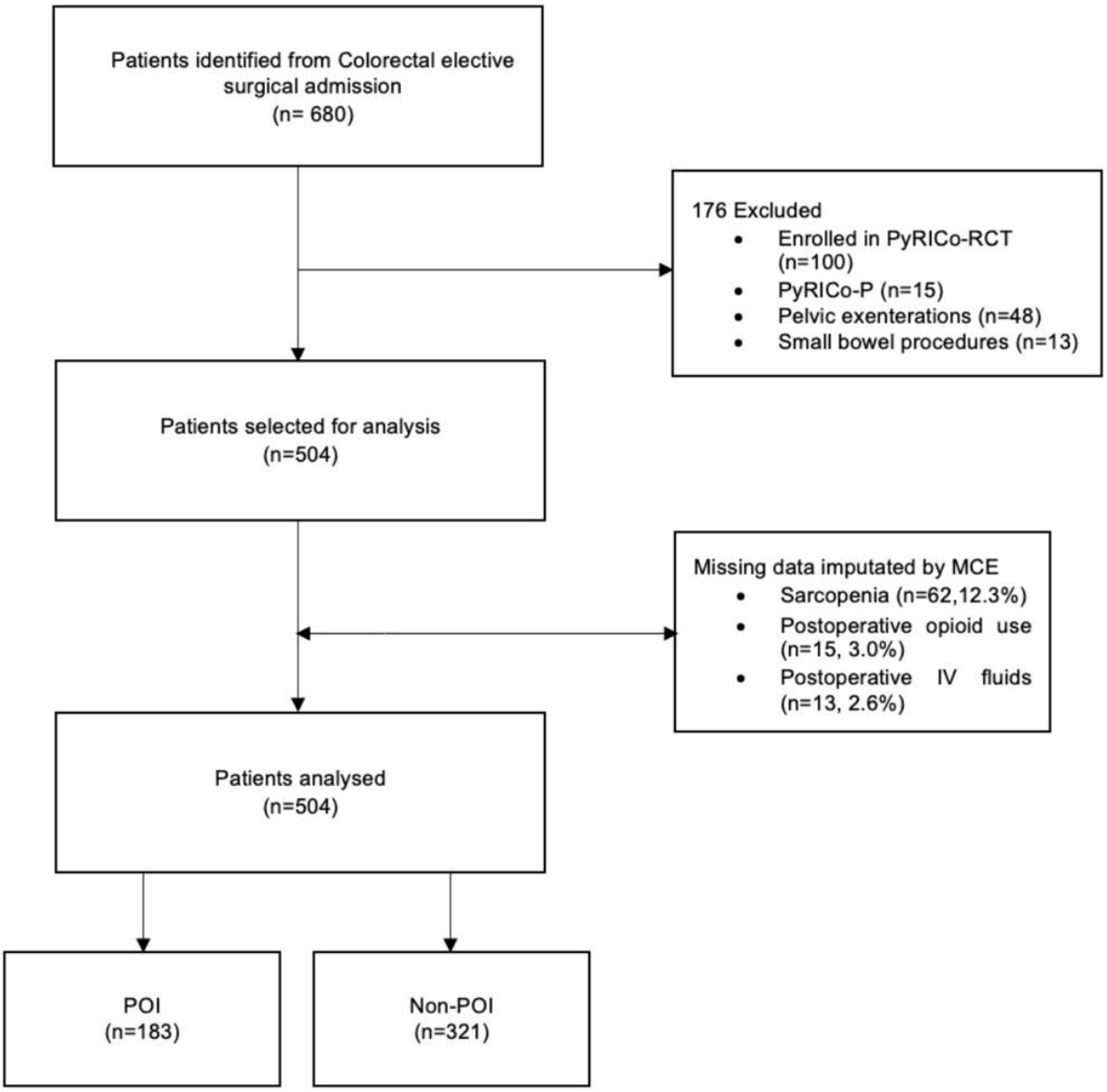

Figure 13. Patient selection flow chart.

Baseline variables are presented in Table 25. Patients diagnosed with POI were more likely to have a smoking history (61.2 vs. 45.5%, p<0.001). No difference in age, ASA scores and sarcopenia were found. Previous abdominal surgery was also more prevalent in the POI group (67.2 vs. 53.9%, p=0.003). No other differences were found in the baseline demographics. An open approach (51.4 vs. 39.9%, p=0.012) and conversion from laparoscopic to open (29.2 vs. 10.9%, p<0.001) were also associated with POI. In addition, patients with POI had increased postoperative opioid use (226 vs. 125 MEQ, p<0.001), and lower postoperative potassium (3.7 vs. 3.8 mmol/L, p=0.002). Patients with POI were also more likely to require intensive care unit (ICU) admission (10.9 vs. 3.1%, p<0.001).

Table 25. Baseline characteristics

Variables	No POI	POI	P value
Demographics			
Age, years	65 (52-74 [18-92])	66 (56-75 [21-94])	0.126
Gender			0.165
Female	136 (42.4)	66 (36.1)	
Male	185 (57.6)	117 (63.9)	
BMI, kg/m^2	27.2 (23.9-31.2 [15.9-62.3]	27.4 (24.2-31.7 [16.0-63.7]	0.381
ASA			0.081
1-2	168 (52.3)	81 (44.3)	
3-4	153 (47.7)	102 (55.7)	
Dependent of activities of daily living	37 (11.5)	21 (11.5)	0.986
Sarcopenia			0.057
No	225 (80.9)	120 (73.2)	
Yes	53 (19.1)	44 (26.8)	
Missing	*43*	*19*	
Smoking history	146 (45.5)	112 (61.2)	**<0.001**
Diabetes Mellitus	69 (21.5)	32 (17.5)	0.280
Congestive cardiac failure	15 (4.7)	5 (2.7)	0.283
Chronic obstructive pulmonary disease	28 (8.7)	25 (13.7)	0.082
Hypertension requiring medication	139 (43.3)	86 (47.0)	0.423
Regular steroid use	10 (3.1)	7 (3.8)	0.671
Preoperative Haemoglobin, g/l	135 (119.5-145 [80-176])	135 (121-148 [74-176])	0.423
Preoperative Total protein, g/l	73 (69-77 [39-95])	73 (69-77 [56-93])	0.979
Preoperative Albumin, g/l	37 (34-40 [19-49])	37 (34-40 [20-49])	0.696
Previous abdominal surgery	173 (53.9)	123 (67.2)	**0.003**
Surgical indication			0.129
Malignancy	198 (61.7)	99 (54.1)	
Diverticular	16 (5.0)	7 (3.8)	
Inflammatory bowel disease	31 (9.7)	14 (7.7)	
Reversal of stoma/restoration of continuity	59 (18.4)	51 (27.9)	
Other (i.e. polyposis, volvulus, stricture.)	17 (5.3)	12 (6.6)	
Operative variables			
Approach			**0.012**
Open	128 (39.9)	94 (51.4)	
Laparoscopic	193 (60.1)	89 (48.6)	
Conversion from laparoscopic to open	21 (10.9)	26 (29.2)	**<0.001**
Operation type			**0.019**
Abdomino-perineal resection	1 (0.3)	4 (2.2)	
Formation of stoma (no resection)	15 (4.7)	3 (1.6)	
Hartmann's procedure	5 (1.6)	7 (3.8)	
Left sided	91 (28.3)	46 (25.1)	
Right sided	114 (35.5)	68 (37.2)	
Reversal of Hartmann's	17 (5.3)	19 (10.4)	
Reversal of ileostomy	43 (13.4)	24 (13.1)	
Total/subtotal colectomy	35 (10.9)	12 (6.6)	
Stoma formed	72 (22.4)	37 (20.2)	0.562
Operative time, min	159 (115-210 [29-433])	166(130-215 [45-385])	0.376
Neuromuscular reversal agent			0.479
Neostigmine/glycopyrrolate	195 (60.7)	117 (63.9)	
Sugammadex/None	126 (39.3)	66 (36.1)	
Intraoperative opioids, MEQ	128 (91-175 [20-806])	126 (93-180 [20-445])	0.588
Postoperative variables			
Postoperative opioids, MEQ	125 (60-243 [0-1292])	226 (106-397 [0-1831])	**<0.001**

Missing	*13*	*2*	
Lowest postoperative potassium, mmol/l	3.8 (3.6-4.1 [2.6-5.7])	3.7 (3.4-4.1 [0.9-4.8])	**0.002**
Intraoperative intravenous fluids, ml	2000(1000-2000 [100-5000])	2000(1000-2000 [158-4000])	0.051
Postoperative (recovery) intravenous fluids, ml *Missing*	1000(500-1300 [0-3700]) *8*	1000(500-1263 [0-3200]) *5*	0.892
Blood transfusion required	19 (5.9)	11 (6.0)	0.967
Intensive care unit admission	10 (3.1)	20 (10.9)	**<0.001**

Values are Median (IQR[Range]) or number (frequency).
ASA, American Society of Anaesthesiologist Physical Status Classification. ADLs, Activities of Daily Living, BMI, Body Mass Index. MEQ, Morphine equivalents.

Table 26 demonstrates the results of the multivariate logistic regression analysis. Smoking history, previous abdominal surgery, conversion to open surgery, postoperative opioid use, postoperative hypokalaemia, and ICU admission were associated with POI on univariate analysis. On multivariate analysis, smoking history (OR 1.88 (95% CI 1.26-2.80), p=0.01), conversion from laparoscopic to open (OR 2.53 (95% CI 1.26-5.10), p=0.01), postoperative opioid use (OR 2.20 (95% 1.48-3.28), p<0.01) and postoperative hypokalaemia (OR 3.27 (95%CI 2.00-5.35) p<0.01) and intensive care unit admission (OR 2.74 (95%CI 1.17-6.41 p=0.02) retained significance. Laparoscopic approach was also protective for POI on univariate and multivariate analysis (OR 0.64 (0.40-0.99), p=0.05).

Table 26. Univariate and multivariate logistic regression analysis predicting POI.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Age, year				
<65	Reference			
≥65	1.22 (0.85-1.76)	0.27		
Sex				
Female	Reference			
Male	1.30 (0.90-1.90)	0.17		
BMI, kg/m^2				
<30	Reference			
≥30	1.28 (0.87-1.89)	0.20		
ASA				
1-2	Reference			
3-4	1.38 (0.96-1.99)	0.08		
Dependence				
No	Reference			
Yes	1.28 (0.76-2.16)	0.36		
Sarcopenia				
No	Reference			
Yes	1.47 (0.96-2.27)	0.08		
Smoking history				
No	Reference		Reference	
Yes	1.89 (1.31-2.74)	**<0.001**	1.88 (1.26-2.80)	**0.01**
Diabetes Mellitus				
No	Reference			
Yes	0.77 (0.49-1.23)	0.28		
Congestive cardiac failure				
No	Reference			
Yes	0.57 (0.21-1.60)	0.29		
Chronic obstructive pulmonary disease				
No	Reference			
Yes	1.66 (0.93-2.94)	0.09		
Hypertension				
No	Reference			
Yes	1.16 (0.81-1.67)	0.42		
Regular steroid use				
No	Reference			
Yes	1.24 (0.46-3.31)	0.67		
Previous abdominal surgery				
No	Reference		Reference	
Yes	1.75 (1.20-2.56)	**0.004**	1.36 (0.87-2.12)	0.17
Malignancy				
No	Reference			
Yes	0.85 (0.59-1.23)	0.40		
Preoperative Haemoglobin, g/l				
≥110	Reference			
<110	0.86 (0.49-1.50)	0.86		
Preoperative Total Protein, g/l				
≥60	Reference			
<60	0.79 (0.27-2.32)	0.67		
Preoperative Albumin, g/l				
≥34	Reference			
<34	1.07 (0.68-1.67)	0.78		
Surgical Approach				
Open	Reference		Reference	
Laparoscopic	0.63 (0.44-0.90)	**0.01**	0.64 (0.40-0.99)	**0.05**
Conversion from to open				
No	Reference		Reference	
Yes	2.37 (1.29-4.34)	**0.01**	2.53 (1.26-5.10)	**0.01**

Left sided resection				
No	Reference			
Yes	0.97 (0.68-1.40)	0.89		
Stoma				
No	Reference			
Yes	0.88 (0.56-1.37)	0.56		
Operative time, min				
≤180	Reference			
>180	0.99 (0.68-1.43)	0.95		
Neostigmine in Neuromuscular reversal				
No	Reference			
Yes	1.14 (0.79-1.67)	0.48		
Intraoperative opioids, MEQ				
≤150	Reference			
>150	1.04 (0.72-1.49)	0.85		
Postoperative opioids, MEQ				
≤162	Reference		Reference	
>162	2.63 (1.81-3.82)	**<0.01**	2.20 (1.48-3.28)	**<0.01**
Postoperative Potassium, mmol/l				
≥3.5	Reference		Reference	
<3.5	3.39 (2.12-5.39)	**<0.01**	3.27 (2.00-5.35)	**<0.01**
Intraoperative fluids, ml				
≤2000	Reference			
>2000	1.18 (0.74-1.89)	0.480		
Postoperative fluids, ml				
≤1000	Reference			
>1000	1.05 (0.73-1.51)	0.81		
Blood transfusion required				
No	Reference			
Yes	1.02 (0.47-2.19)	0.97		
Intensive care unit admission				
No	Reference		Reference	
Yes	3.82 (1.75-8.34)	**<0.001**	2.74 (1.17-6.41)	**0.02**

ASA, American Society of Anaesthesiologist Physical Status Classification. BMI, Body Mass Index. COPD, Chronic obstructive pulmonary disease MEQ, Morphine equivalents. NM, Neuromuscular.

The MLP neural network model with the highest AUROC (Figure 14) included: ICU admission, postoperative opioid use, postoperative hypokalaemia, sarcopenia, and conversion from laparoscopic to open as the top 5 most predictive variables for POI. The decision tree model (Figure 15) with the highest AUROC showed the highest predictive variables for POI were postoperative hypokalaemia, increased postoperative opioid use, smoking history and male gender. The RBF neural network model with the highest AUROC (Figure 16) included: postoperative and intraoperative opioid use, previous abdominal surgery, smoking history, and postoperative hypokalaemia as the top 5 most predictive variables for POI.

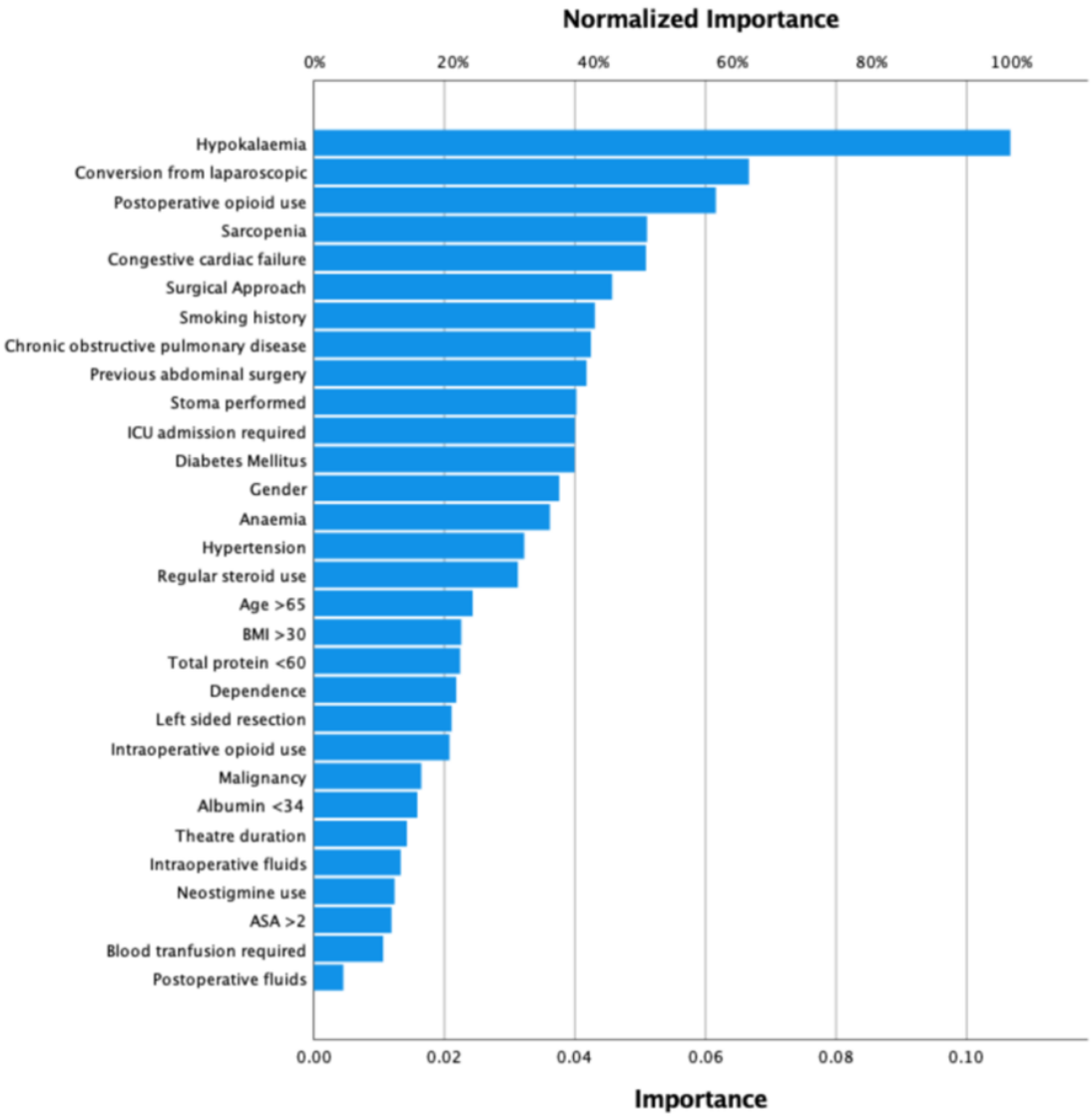

Figure 14. Multilayer perceptron (MLP) variable importance chart.

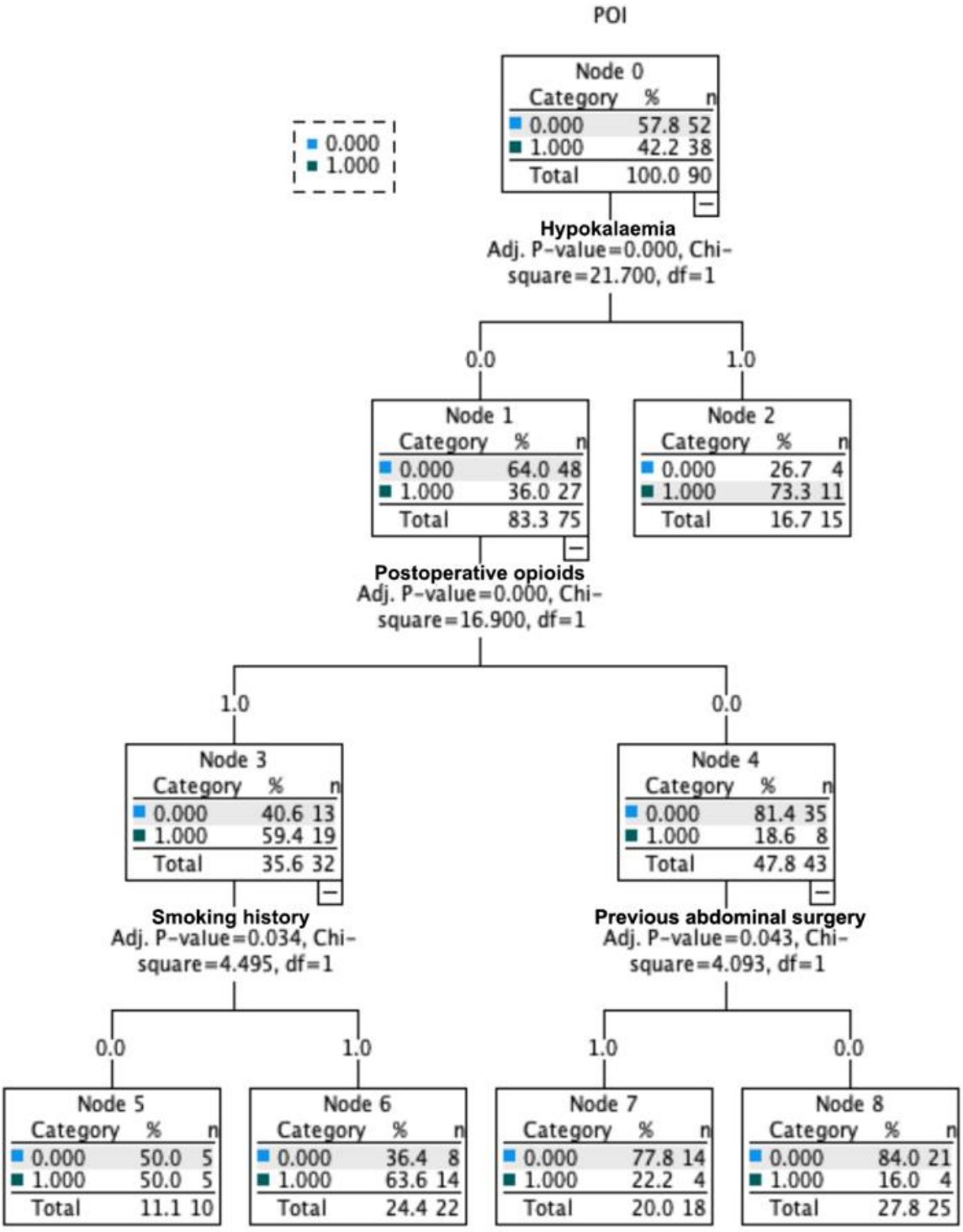

Figure 15. Decision tree analysis testing model.

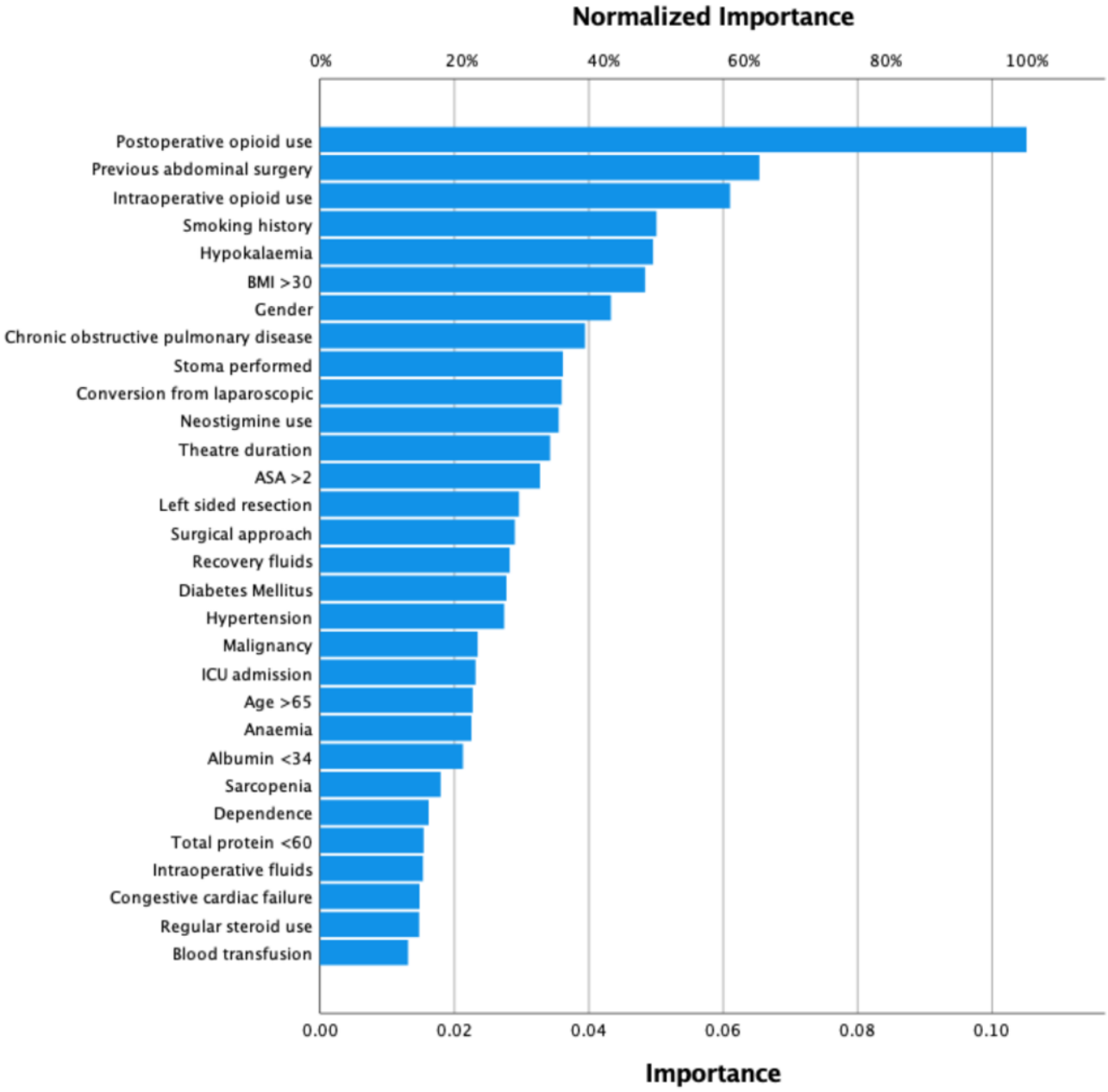

Figure 16. Radial Basis Function (RBF) variable importance chart.

Table 27 demonstrates the model discrimination for the testing cohort. MLP performed the best (AUROC 0.800, 95%CI 0.760-0.840) followed by multivariate logistic regression (AUROC 0.722, 95%CI 0.677-0.767), RBF (AUROC 0.712, 95%CI 0.665-0.758) and finally decision tree models (AUROC 0.706, 95%CI 0.659-0.753). The ROC curves are displayed graphically in Figure 17. The MLP model also demonstrated the highest specificity (98.08% (95%CI 89.74-99.95)), sensitivity (43.33% (95%CI 25.46-62.57)) positive predictive value (92.86% (95%CI 64.13-98.95)) and negative predictive value (75.00% (95%CI 68.64-80.44)), scoring highest in overall model quality (Figure 18).

Table 27. Model discrimination of the testing cohort

	Multilayer Perceptron	**Multivariate Logistic Regression**	**Radial Base Function**	**Decision tree**
AUROC (95%CI)	0.800 (0.760-0.840)	0.722 (0.677-0.767)	0.712 (0.665-0.758)	0.706 (0.659-0.753)
Sensitivity (%, 95%CI)	43.33 (25.46-62.57)	42.08 (34.83-49.58)	30.30 (15.59-48.71)	28.95 (15.42-45.90)
Specificity (%, 95%CI)	98.08 (89.74-99.95)	86.29 (82.04-89.86)	85.07 (74.26-92.60)	92.31 (81.46-97.86)
Positive predictive value (%, 95%CI)	92.86 (64.13-98.95)	63.64 (55.89-70.73)	50.00 (31.62-68.38)	73.33 (48.66-88.86)
Negative predictive value (%, 95%CI)	75.00 (68.64-80.44)	72.32 (69.63-74.87)	71.25 (65.95-76.02)	64.00 (58.85-68.85)

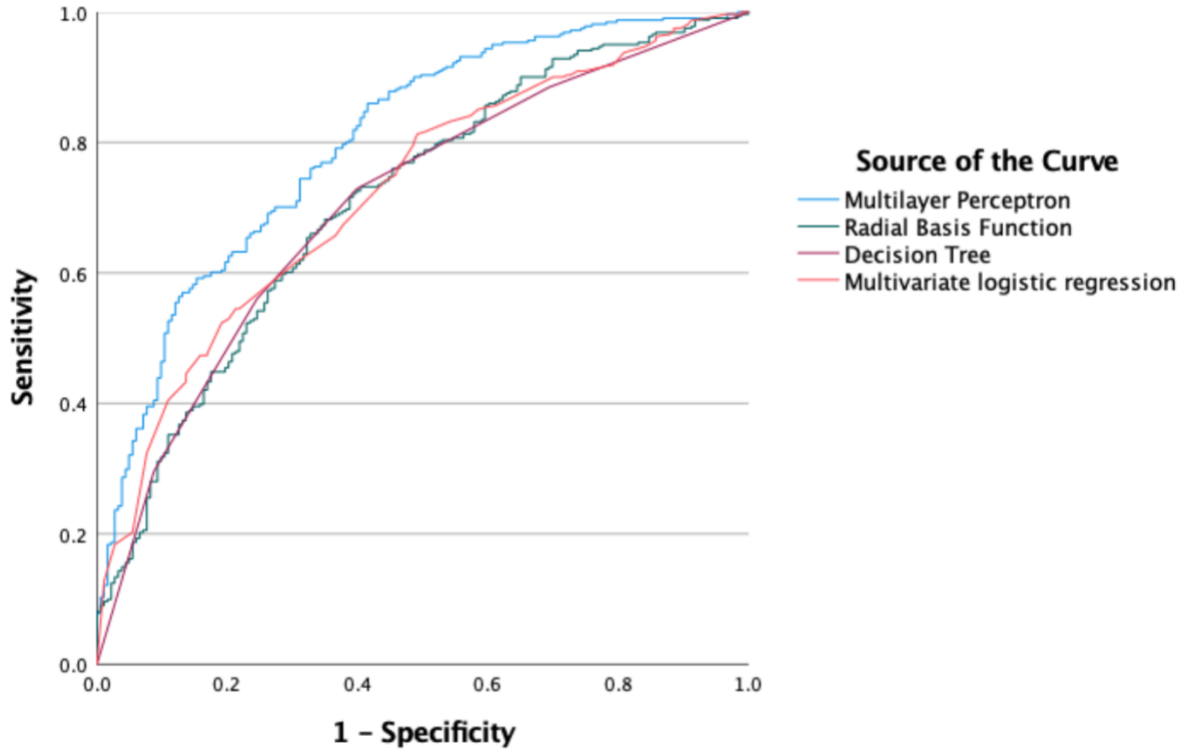

Figure 17. Receiver operating curve graphs for prediction models.

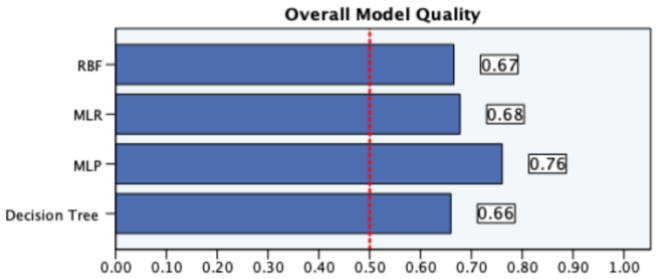

Figure 18. Overall model quality.

A ‘good’ model quality is indicated by model score being over 0.5.

8.5 DISCUSSION

Our findings showed that the MLP model outperformed the RBF, decision tree model and multivariate logistic regression analysis for predicting POI. In addition, the MLP model identified sarcopenia (ranked 4/30) as an important variable for predicting POI.

The use of ML models in healthcare has been increasing to analyse large amounts of data and improve prediction models.[105] Compared to more traditional statistical modelling methods such as logistic regression, ML models do not need to adhere to statistical assumptions, making them more flexible and potentially more accurate.[309] Furthermore, they can rank variables of importance, allowing for a more comprehensive data analysis.[309] In our study, we found that MLP can effectively model complex, non-linear relationships between predictors and outcomes, resulting in improved accuracy compared to logistic regression and decision tree modelling.[309, 310] Regression models have reduced accuracy as they rely on human intervention and subject knowledge for model specification, which makes them less reliable.[310] Furthermore, MLP provides a more accurate model than decision tree models, due to decision trees' dependence on observed data and sequential nature.[311] MLP modelling has been shown to have the lowest error rate and highest accuracy compared to decision trees and logistic regression models.[311] When compared to RBF and its high accuracy, strong tolerance to input noise, and fast convergence, MLP outperformed it in every metric tested.[312] While ML models have been used to predict the risk of metastasis and complications in colorectal surgery, there remains a gap in the literature on their use to predict POI, which was successfully filled by the present study.[109]

The present study was conducted on our available electronic medical records from our hospital and found several factors associated with the development of POI, including

admission to the ICU, open surgical approach, hypokalaemia, and opioid use. POI is a common occurrence in critically ill patients admitted to the ICU. It is thought to be caused by the interaction between the gastrointestinal tract and the immune system.[100, 313] Electrolyte imbalances, such as hypokalaemia, predict POI and can impair smooth muscle contraction and neural activity.[84, 313, 314] Additionally, patients in the ICU often receive medications that impair gastrointestinal tract motility, such as opioids and neuromuscular-blocking agents, which are known to increase the incidence of POI by decreasing the amplitude and frequency of smooth muscle contraction in the colon.[84, 313, 314] Intravenous opioids in the first 48 hours postoperatively have been recognised as a strong predictor of POI, regardless of the duration or amount.[100] Previous studies have looked at the administration of opioid antagonists via enteral route to prevent POI with varied success.[100, 147] Our study also found that a laparoscopic surgical approach was protective against POI, as it has been associated with a shorter duration of POI. Nonetheless, it is still being determined if this is due to the surgical technique itself or other factors such as lower blood loss and shorter time to detection of peristalsis.[14, 63, 314] Our study suggests that a minimally invasive surgical approach, opioid reduction, and correction of electrolyte abnormalities are important modifiable risk factors to reduce POI.

In this retrospective analysis, we identified a rate of POI at 36% which surpasses the rate reported in previous studies (10-35%).[130, 261, 284] However, this rate aligns with our historical average of 30-35%.[261, 303, 304] This observation may be attributed to variations in the definitions of POI used across different studies, or possibly due to an under-reporting of POI in previous literature. The high incidence of POI likely stems from our research group's specific focus on POI, our utilization of a broad colorectal cohort and a stringent POI definition, as by the validated outcome measure GI-2.

A newly identified risk factor for POI on the MLP was sarcopenia, characterised by the progressive loss of skeletal muscle mass and quality, often associated with age.[315, 316] This condition is becoming increasingly prevalent in colorectal cancer patients, affecting 37% and significantly prolonging hospital stays and postoperative complications.[317] Despite the growing awareness of sarcopenia, limited papers investigate its link to POI.[303, 318] The relationship between sarcopenia and POI is likely multifactorial, relating to nutritional imbalances that cause a pro-inflammatory state, impairing the macrophage response to peritoneal irritation and poor smooth muscle contractility in the intestinal plexus.[318, 319] Currently, no strategies to improve POI using prehabilitation exist. Previous prehabilitation programs in colorectal surgery have proven ineffective in reducing postoperative outcomes, but most target a malignant patient population.[320] We suggest that targeting the non-malignant population, where the malabsorption and catabolic effects mediated by malignancy are not driving sarcopenia, may be more effective in improving postoperative outcomes.[321] Given POI is the most prevalent postoperative complication following colorectal surgery, this area could be investigated further.

The potential of this study lies in utilising the information provided by a broad assessment of patients undergoing colorectal surgery, despite the inherent limitation of heterogeneity in surgical indication and procedural type. The approach enabled us to identify potential risk areas for POI within colorectal surgery, rather than focusing solely on a subset of colorectal surgical patients. The subsequent phase of this study involves using the insights obtained from the MLP as the foundation to create a nomogram, enabling us to have a tool to identify patients at the highest risk of POI and focus our efforts on improving their postoperative recovery, particularly avoiding the complications of undertreating POI such as aspiration pneumonia and malnutrition.

This study has some limitations. Firstly, it is a retrospective study conducted in a single centre that is inherent of selection bias and small sample size. However, the data used in this study was of robust quality, with minimal missing data. Secondly, there is no external validation cohort to further validate the results. A larger multicentred cohort may have resulted in more accurate findings. Moreover, identifying risk factors for POI is challenging secondary to the difficulty of defining POI, along with our rate of open surgical cases, impacts our overall prevalence of POI. However, adhering to a strict clinical definition of POI is a strength of our study. Finally, the present study provides evidence that ML can facilitate the identification of predictive variables with a smaller sample size.

8.6 CONCLUSION

This study suggests that MLP outperformed RBF, logistic regression, and decision tree models in predicting POI, indicating that ML has the potential to provide valuable insights into the importance and ranking of specific predictive variables. Our findings highlighted several modifiable risk factors for POI, such as sarcopenia. Further investigation of these factors could potentially lead to the development of targeted interventions to prevent POI, ultimately improving patient outcomes.

SYNOPSIS

This thesis consists of 8 chapters that enhances the understanding of ACIs in abdominal surgery, elucidates the financial implications of POI, establishes the efficacy of pyridostigmine in improving GI function after surgery, and identifies potential risk factors and future strategies for enhancing GI recovery postoperatively. The chapters encompass literature reviews, systematic reviews and meta-analyses, retrospective cohort studies, machine learning models, and a novel double blinded RCT, addressing the questions raised by the introduction and providing insights to guide further research in this area.

In the introduction, I offer a concise overview of the burden of POI following colorectal surgery. By examining the incidence, risk factors and pathophysiology, I emphasise that POI represents the most significant complication following abdominal surgery, particularly colorectal surgery. I highlight the considerable morbidity and financial burden associated with POI while noting a need for comprehensive Australian and global data. Furthermore, I discuss current preventative strategies for POI, which have varied success but fail short of correcting the autonomic imbalance by which POI occurs. The introduction then examines the use of ACIs in surgery, specifically their roles in neuromuscular reversal and their potential to improve GI recovery by modulating the CAIP. To provide contextual understanding for the subsequent chapters, I also discuss risk factors for POI, the potential to use machine learning to uncover further associations, and the role of sarcopenia in colorectal surgery as a predictor of complications.

This thesis describes novel insights into the following questions raised by our introduction:

- Do ACIs impact GI recovery when administered for neuromuscular reversal during anaesthesia?
- What are the financial implications of POI?

- What is the efficacy of adding pyridostigmine following colorectal surgery in restoring GI function?
- Can machine learning identify additional risk factors for POI?

The questions raised were further interrogated in subsequent chapters. **Chapter 2** presents a clinical review of the literature that summarises the current applications of ACIs in abdominal surgery. The chapter provides a brief overview of how ACIs used in neuromuscular reversal during anaesthesia could impact GI motility and the use of ACIs to resolve ACPO. Finally, this chapter highlights the use of ACIs in preventing or treating POI, underscoring the need for RCTs in this area.

Building upon the literature review, **Chapter 3** systematically examines RCTs investigating the use of ACIs to improve GI recovery after abdominal surgery. Of eight published RCTs involving 703 patients, five studies showed a statistically significant reduction in time to return of GI function using the ACIs neostigmine and pyridostigmine. However, variations in methodology, procedure type, and concerns for bias were observed. Despite these variations, the evidence supports using ACIs to improve GI function recovery post-abdominal surgery. This highlighted the need for an RCT embedded in an ERP, especially for colorectal surgery patients.

Chapter 4 provides further evidence and our local experience of the impact of neuromuscular reversal agents (sugammadex or neostigmine/glycopyrrolate) used during general anaesthesia on GI recovery, focusing on colorectal surgery. This chapter examines the largest cohort (n=335) of colorectal surgical patients investigating the impact of neostigmine/glycopyrrolate and sugammadex use on GI recovery. Our findings suggest sugammadex use is associated with a shorter time to first stool (median (range) 2(0-10)

vs. 3(0-12) days, p=0.035) and GI-2 (median 3(0-10) vs. 3(0-12) days, p=0.036), likely owing to the glycopyrrolate co-administered with neostigmine. The multivariate analysis also found bowel anastomoses and increased postoperative opioid use ($p<0.05$) remained predictive of time to GI-2. However, the selection of neuromuscular reversal agents does not significantly impact the development of POI in our cohort of patients.

Chapter 5 reports the cost of POI after colorectal surgery in an Australian public hospital. The analysis of over 400 patients highlights that POI, present in 35% of our cohort, is associated with a 26.4% increase in the total cost of inpatient care. POI was associated with increased length of stay and higher rates of complications such as pneumonia. The most significant determinants of increased total hospital costs were POI, elderly patients, stoma formation, large bowel surgery, prolonged theatre time, complications, and length of stay. Providing a broader perspective, **Chapter 6** presents the first systematic review and meta-analysis examining the financial impact of POI on the total cost of inpatient stay, demonstrating a 66.3% increase in total hospital costs or €8,233. Colorectal-specific studies indicate a €7,242 increase or 57.3% in total hospital costs. However, there was significant heterogeneity in the data. Annually, in the USA, I estimate POI increases total hospital costs by €3.9 billion. I also highlight the need for multicentre data using a uniform POI definition, underscoring the significant global financial burden of POI following abdominal surgery and the importance of focusing efforts on reducing the incidence of POI with adjunctive therapies.

Chapter 7 outlines the methodology and results of our novel double blinded RCT to address the primary aim of this thesis. The study evaluates the addition of pyridostigmine 60mg twice daily within the current ERP following elective colorectal surgery. The RCT involved 18 months of recruitment to reach 130 adult patients, 129 of whom received

pyridostigmine or placebo as per randomisation. I showed a significant reduction in GI-2 by one day (median [IQR] 2[1-3] vs. 3[2-4]; p=0.015). However, no significant differences were observed in POI, length of hospital stay, or 30-day complications. Furthermore, there were no significant differences in anastomotic leak, cardiac complications, or patient-reported side effects. This high-quality RCT supports our hypothesis that adding pyridostigmine to an ERP following elective colorectal surgery improves GI recovery.

Chapter 8 describes machine learning techniques to identify new risk factors for POI, aiming to guide modifiable strategies. Through a 504-patient retrospective cohort study, multivariate logistic regression, radial basis function (RBF), decision trees, and multilayer perceptron (MLP) models were trained and tested to predict POI. The MLP model outperformed (AUROC 0.800, 95%CI 0.760-0.840) the multivariate logistic regression (AUROC 0.722, 95%CI 0.677-0.767), RBF (AUROC 0.712, 95%CI 0.665-0.758) and decision tree models (AUROC 0.706, 95%CI 0.659-0.753). The MLP model also identified sarcopenia as a potential modifiable risk factor for POI. This study highlights the potential of machine learning to identify specific predictive variables for POI and guide targeted prevention strategies.

CONCLUSIONS

Considering the research presented in this thesis, several conclusions can be drawn:

POI represents a significant problem post-surgery, increasing morbidity and the cost of inpatient stays. Globally, the total cost of hospital stay increases by 66%. However, there is considerable heterogeneity among studies. This information is valuable when evaluating the cost-effectiveness of future strategies to prevent POI.

The evidence for using pyridostigmine to improve GI recovery before this thesis was lacking. I showed that neostigmine use as part of neuromuscular reversal delays the time to first stool; however, it has a limited impact on the development of POI. Our innovative double blinded RCT found pyridostigmine was well-tolerated, appeared safe, and improved GI recovery post colorectal surgery.

Machine learning was also demonstrated to offer valuable insights into the significance and ranking of specific predictive variables for POI over traditional statistical methods. In addition to well-established associations, such as postoperative opioid use and hypokalaemia, a novel association between sarcopenia and POI was identified.

FUTURE DIRECTIONS

To further validate the improvements observed in GI recovery from the RCT conducted as part of this thesis, I recommend expanding this trial to encompass a multi-centred RCT. This expansion would provide increased numbers to power for other outcome measures, and enhance the generalisability of the findings. Furthermore, future research should explore the use of this intervention following other types of abdominal surgery to assess its potential benefits across different operations where POI remains a significant issue. Additionally, there is scope to pool data from this trial to further evaluate the impact of laxatives[235] and medications to enhance GI motility[147] and whether this impacts complications such as anastomotic leak. Moreover, I expected to see an improvement in length of stay with improved GI recovery but this was not the case. Further research into the reasons for delayed discharge is required.

In addition, from the observations made during our study and the previous literature, emphasis is placed on patient morbidity and the financial aspects when examining strategies to improve POI. It is essential also to address the need for validated patient-reported outcome measures in these studies. Further work in this area is required, and I look forward to the valuable insight provided by the Patient-Reported Outcome in Digestive Diseases (PRO-diGI) study.[322]

Regarding sarcopenia, moving forward it is important to consider the financial impact of sarcopenia, and evaluate the cost-effectiveness of future prehabilitation programmes. Given the newfound association between sarcopenia and POI, future studies investigating the impact of prehabilitation on sarcopenia should include POI as a key outcome.

APPENDIX – A:

SUPPLEMENTARY MATERIAL FOR USE OF ACETYLCHOLINESTERASE INHIBITORS IN REDUCING TIME TO GASTROINTESTINAL FUNCTION RECOVERY FOLLOWING ABDOMINAL SURGERY: A SYSTEMATIC REVIEW.

PRISMA 2020 MAIN CHECKLIST

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p. 4, Table S1.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 4,5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 4,5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 4,5

Topic	No.	Item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	p. 5.
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 6, Fig 1.

Topic	No.	Item	Location where item is reported
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig 1.
Study characteristics	17	Cite each included study and present its characteristics.	p. 6,7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 7-8, Fig 2-3.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	p. 6-10, Table 1-4.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p. 7,8. Fig 1-3.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N.A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N.A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p. 7, Fig 2-3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p. 7-8, Fig 2-3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p 10-11
	23b	Discuss any limitations of the evidence included in the review.	p. 11
	23c	Discuss any limitations of the review processes used.	p. 11
	23d	Discuss implications of the results for practice, policy, and future research.	p. 11-12
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 4

Topic	No.	Item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p. 4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N.A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p. 1
Competing interests	26	Declare any competing interests of review authors.	p. 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	p. 6-9, Table 1-4.

PRIMSA ABSTRACT CHECKLIST

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Search strategy

Data base	Search Terms	No. of results
Pub med	(((((((postoperative ileus[Title/Abstract]) OR (post-operative ileus[Title/Abstract])) OR (post operative ileus[Title/Abstract])) OR (ileus[Title/Abstract])) AND (Neostigmine[Title/Abstract])) OR (pyridostigmine[Title/Abstract])) OR (acetylcholinesterase inhibitor[Title/Abstract])) AND (surgery[Title/Abstract])	165
EMBASE	((neostigmine or pyridostigmine or acetylcholinesterase inhibitor) and ileus).af	334
Medline EBSCO	MH ileus AND (TX Pyridostigmine OR TX Acetylcholinesterase inhibitor OR TX Neostigmine) AND (TX postoperative OR TX surgery OR TX post operative OR TX postoperative)	40
MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (Ovid)	((neostigmine or pyridostigmine or acetylcholinesterase inhibitor) and ileus).af.	90
CENTRAL/CCTR	((neostigmine or pyridostigmine or acetylcholinesterase inhibitor) and ileus).af.	34
Cochrane	((neostigmine or pyridostigmine or acetylcholinesterase inhibitor) and ileus).af	30
CIANHL	(TX postoperative ileus or paralytic ileus or ileus or bowel motility) AND (TX pyridostigmine OR TX acetylcholinesterase inhibitor OR neostigmine)	71
Clinical trials.gov	Ileus OR postoperative ileus OR bowel | Neostigmine OR pyridostigmine OR acetylcholinesterase inhibitor	12

APPENDIX – B:

SUPPLEMENTARY MATERIAL FOR EFFECT OF NEUROMUSCULAR REVERSAL WITH NEOSTIGMINE/GLYCOPYRROLATE VERSUS SUGAMMADEX ON POSTOPERATIVE ILEUS FOLLOWING COLORECTAL SURGERY

Strobe statement

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3,4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5,6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5,6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6 + Figure 1
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	10-11
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
	12	(*a*) Describe all statistical methods, including those used to control for confounding	6

Statistical methods		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	Reported in tables
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1.
		(b) Give reasons for non-participation at each stage	Fig 1.
		(c) Consider use of a flow diagram	Fig 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1+3. Summarised p7
		(b) Indicate number of participants with missing data for each variable of interest	Table 1 and 3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N.A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Table 2.
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Table 3 and 4
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

APPENDIX – C:

SUPPLEMENTARY MATERIAL FOR COST OF POSTOPERATIVE ILEUS FOLLOWING COLORECTAL SURGERY: A COST ANALYSIS IN THE AUSTRALIAN PUBLIC HOSPITAL SETTING.

Supplementary table

Patient Label		Surgery Type	Colorectal Surgery Open
		Surgeon	Enhanced Recovery after Surgery
		Date of surgery	/ /

Stage	Standard	Completed. Staff to sign.	If NOT completed, give reason.
Pre-Operative Date:	Bowel preparation: Picolax x 2 for L sided cases, Fleet enema for R sided cases		
	In patients with colorectal cancer: Screen for and treat Fe defficiency + 3 drinks daily of immunonutrition for 5 days preop. Reduced starvation (food up to 6h pre-op, carbohydrate drink 2h pre-op). 2 x carbohydrate loading drinks morning of surgery (before 0600). NB. Caution in patients with delayed gastric emptying (e.g. diabetics).		
	Pre-emptive high risk physician review if concerns re frailty or morbidity. Document end of life wishes.		
	Education about discharge goals and arrange post-discharge support pre-emptively. Education about expected post-op pain and aims of analgesia (move and deep breathe), and that some discomfort is expected.		
	Antibiotic prophylaxis (CALHN guidelines) Cefazolin 2g IV + Gentamicin 2mg/kg IV + Metronidazole 500mg IV (OR Ceftriaxone 1g IV + Metronidazole 500mg IV, if eGFR < 60) (OR Vancomycin 1g IV instead of Cefazolin, if penicillin / cef allergy)		
	Regional blocks Mid-Thoracic epidural (T6-T10), if medical indication only. If no epidural used => 0.25% Levobupivacaine TAP block at start of case under direct vision AND TAP catheter continuous infusion (2 x 0.25% levobupivacaine infusors, 5ml/h, start at end of case). Surgeon to prescribe levobupivacaine infusion at end of case in patient chart. Lignocaine intra-operative infusion and IPLA can also be considered - coordinate dosing between surgical and anaesthetic team.		
	IV fluids Euvolaemic regimen using balanced solution (plasmalyte or hartmann's). 1 - 2L expected total IV fluid volume during routine colorectal case. Additional replacement of blood loss at the discretion of the anaesthetist and surgeon (suggest colloid or blood depending on volume required).*		
	Antiemetics (CALHN guidelines) Dexamethasone / Ondansetron / Droperidol		
	Analgesia Maximise opioid sparing techniques.		
	Under body warmer, warm air blanket if temp < 36 degrees Body temp monitoring catheter. Bladder IDC optional for right hemicolectomy.		
	TEDS and SCD (remove SCD at end of case) Clexane 40mg sc if no increased bleeding risk (use 20mg if wt < 50kg or CrCl < 30)		
	Consider intra-op orogastric tube to be removed at the end of case.		
	No routine peritoneal drains. No routine postop nasogastric tube. If IDC inserted for right hemicolectomy, consider removal at the end of case.		
Post op day 0 - recovery then ward Date:	Warming blanket to continue in recovery if temp <36 degrees		
	Oxygen supplementation as required to maintain SpO2 >95% (even if patient asleep).		
	Hourly breathing + coughing (I-COUGH resp bundle: https://tinyurl.com/yctev9x4)		
	IV fluids 4%Dex / 0.18%NaCl + 30KCL running at 50ml/h. Stop IV fluids completely if patient tolerating oral intake on the night of surgery. Urine output ≥ 20ml/h averaged over 4h is acceptable, avoid bolusing		
	Antiemetics Ondansetron 4mg IV Q8h regular Maxolon 10mg IV Q8h regular: Do not use in patients > 75 years old.		
	Analgesia Paracetamol 1g PO Q6h regular: Caution in patients < 60kg or with liver dysfunction. Tramadol 50mg PO/subcut Q4h regular: Do not use if on SSRI or eGFR < 60. Coloxyl + Senna 1 tab BD, MgOH2 10ml BD Anaesthetist to consider PCA +/- Ketamine infusion if required.		
	Oral intake Free oral fluids from 4 hours after surgery => limit to 1000ml in first 12 hours. Fortijuce/Sustagen/Resource drink from 4 hours following completion of operation. Regular diet for dinner if fluids tolerated and no nausea. Stop drinking if nausea or vomiting or hiccuping. Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)		

	Aim for placement in WARD 5E If morning surgery and patient returns to the ward prior to 1800 => sit out of bed.		
Post Op Day 1 Date:	Continue Clexane 40mg sc until discharge (use 20mg if wt < 50kg or CrCl < 30) Continue TEDS until discharge		
	If IDC in consider removal after medical review. NB. Decision for removal will be based on the type of surgery.		
	Hourly breathing + coughing (I-COUGH resp bundle: https://tinyurl.com/yctev9x4)		
	Antiemetics Ondansetron 4mg IV Q8h regular Maxolon 10mg IV Q8h regular: Do not use in patients > 75 years old.		
	Analgesia Paracetamol 1g PO Q6h regular: Caution in patients < 60kg or with liver dysfunction. Tramadol 50mg PO/subcut Q4h regular: Do not use if on SSRI or eGFR < 60. Coloxyl + Senna 1 tab BD, MgOH2 10ml BD (Fleet enema OD for right colectomy) Continue PCA or epidural analgesia if this was started.		
	Oral intake General diet as tolerated. Fortijuce/Sustagen/Resource drink BD. Stop drinking if nausea or vomiting or hiccuping. Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)		
	Sit out of bed for meals 4 hours in chair during the day. May be split up.		
	60 metre walk (1st) 60 metre walk (2nd) **No bedpans or urinals.** Epidural analgesia or PCA must NOT stop the patient from walking.		
Post op Day 2 Date:	**Remove epidural or PCA** (if tolerating oral intake)		
	Potential for IDC removal after medical review		
	Hourly breathing + coughing (I-COUGH resp bundle: https://tinyurl.com/yctev9x4)		
	Antiemetics Ondansetron 4mg PO / IV Q8h regular Maxolon 10mg PO / IV Q8h regular: Do not use in patients > 75 years old.		
	Analgesia Paracetamol 1g PO Q6h regular: Caution in patients < 60kg or with liver dysfunction. Tramadol 50mg PO Q4h regular: Do not use if on SSRI or eGFR < 60. Coloxyl + Senna 1 tab BD, MgOH2 10ml BD (Fleet enema OD for right colectomy)		
	Oral intake General diet as tolerated. Fortijuce/Sustagen/Resource drink BD. Stop drinking if nausea or vomiting or hiccuping. Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)		
	Sit out of bed for all meals 6 hours in chair during the day. Split up.		
	60 metres walk (1st) 60 metres walk (2nd) 60 metres walk (3rd) 60 metres walk (4th) **No bedpans or urinals.** Epidural analgesia or PCA must NOT stop the patient from walking.		
Post op Day 3 Date:	Order medications for discharge tomorrow		
	Hourly breathing + coughing (I-COUGH resp bundle:		
	Antiemetics Ondansetron 4mg PO / IV Q8h regular Maxolon 10mg PO / IV Q8h regular: Do not use in patients > 75 years old.		
	Analgesia - Consider changing analgesia to prn if pain controlled Paracetamol 1g PO Q6h regular: Caution in patients < 60kg or with liver dysfunction. Tramadol 50mg PO Q4h regular: Do not use if on SSRI or eGFR < 60. Coloxyl + Senna 1 tab BD, MgOH2 10ml BD (Fleet enema OD for right colectomy)		
	Oral intake General diet as tolerated. Fortijuce/Sustagen/Resource drink BD. Stop drinking if nausea or vomiting or hiccuping. Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)		
	Sit out of bed for all meals 8 hours in chair. Split up.		
	60 metre walk (1st) 60 metre walk (2nd) 60 metre walk (3rd) 60 metre walk (4th) 100 metre walk (1st) 100 metre walk (2nd)		
Post op Day 4 - Home Date:	Discharge patient if discharge criteria met. If not met, repeat instructions for Day 3. See 'Criteria for discharge' below		
	100 metre walk (1st) 100 metre walk (2nd) 100 metre walk (3rd) 100 metre walk (4th) Can be discharged prior to completion of walks.		
	Oral analgesia / antiemetics take home.		

	Medical Staff please note criteria for safe discharge.		
Medical Staff Criteria for safe discharge	No clinical and biochemical concern		
	Tolerance of general diet		
	Passing flatus OR bowels opened.		
	Acceptable pain control on oral analgesia.		
	Mobilising independently.		
	If stoma present: patient managing care independently.		

*https://www.uptodate.com/contents/intraoperative-fluid-management
NB: all medications recommended should only be prescribed if no absoulte or relative contra-indication. This is the responsibility of the prescribing physican.
This a suggested guideline only, and may not apply to all patients. Individualised treatment is still required, including earlier discharge if clinically safe.

Patient Label	Surgery Type	**Colorectal Surgery** **Lap / Robot** **Enhanced Recovery after Surgery**
	Surgeon	
	Date of surgery	/ /

Stage	Standard	Completed. Staff to sign.	If NOT completed, give reason.
Pre-Operative Date:	Bowel preparation: Picolax x 2 for L sided cases, Fleet enema for R sided cases		
	In patients with colorectal cancer: Screen for and treat Fe defficiency + 3 drinks daily of immunonutrition for 5 days preop. Reduced starvation (food up to 6h pre-op, carbohydrate drink 2h pre-op). 2 x carbohydrate loading drinks morning of surgery (before 0600). NB. Caution in patients with delayed gastric emptying (e.g. diabetics).		
	Pre-emptive high risk physician review if concerns re frailty or morbidity. Document end of life wishes.		
	Education about discharge goals and arrange post-discharge support pre-emptively. Education about expected post-op pain and aims of analgesia (move and deep breathe), and that some discomfort is expected.		
	Antibiotic prophylaxis (CALHN guidelines) Cefazolin 2g IV + Gentamicin 2mg/kg IV + Metronidazole 500mg IV (OR Ceftriaxone 1g IV + Metronidazole 500mg IV, if eGFR < 60) (OR Vancomycin 1g IV instead of Cefazolin, if penicillin / cef allergy)		
	Regional blocks 0.25% Levobupivacaine TAP block at start of case under direct vision AND TAP catheter continuous infusion (2 x 0.25% levobupivacaine infusors, 5ml/h). Lignocaine intra-operative infusion and IPLA can also be considered - coordinate dosing between surgical and anaesthetic team.		
	IV fluids Euvolaemic regimen with balanced solution (plasmalyte or hartmann's). 1 - 2L expected total IV fluid volume during routine colorectal case. Additional replacement of blood loss at the discretion of the anaesthetist and surgeon (suggest colloid or blood depending on volume required).*		
	Antiemetics (CALHN guidelines) Dexamethasone / Ondansetron / Droperidol		
	Analgesia Maximise opioid sparing techniques.		
	Under body warmer, warm air blanket if temp < 36 degrees Body temp monitoring catheter. Bladder IDC optional for right hemicolectomy.		
	TEDS and SCD (remove SCD at end of case) Clexane 40mg sc if no increased bleeding risk (use 20mg if wt < 50kg or CrCl < 30)		
	Consider intra-op orogastric tube to be removed at the end of case.		
	No routine peritoneal drains. No routine postop nasogastric tube. If IDC inserted for right hemicolectomy, consider removal at the end of case.		
Post op day 0 - recovery then ward Date:	Warming blanket to continue in recovery if temp <36 degrees		
	Oxygen supplementation as required to maintain SpO2 >95% (even if patient asleep)		
	Hourly breathing + coughing (I-COUGH resp bundle: https://tinyurl.com/yctev9x4)		
	IV fluids 4%Dex / 0.18%NaCl + 30KCL running at 50ml/h. Stop IV fluids completely if patient tolerating oral intake on the night of surgery. Urine output ≥ 20ml/h averaged over 4h is acceptable, avoid bolusing		
	Antiemetics Ondansetron 4mg IV Q8h regular Maxolon 10mg IV Q8h regular: Do not use in patients > 75 years old.		
	Analgesia (see Appendix 1 for exclusions) Paracetamol 1g PO Q6h regular: Caution in patients < 60kg or with liver dysfunction. Pregabalin 75mg PO BD regular (50mg if > 70 yrs): Do not use if eGFR < 60. Coloxyl + Senna 1 tab BD, MgOH2 10ml BD Tramadol 50mg PO/subcut Q4h / PRN: Do not use if on SSRI or eGFR < 60. Avoid opioids completely if possible (contact surgical team if opioids required). If needed, then recommend half the age-based dosing and PCA as last resort. If PCA is required, stop pregabalin and refer to APS.		

F	**Oral intake** Free oral fluids from 4 hours after surgery => limit to 1000ml in first 12 hours. Fortijuce/Sustagen/Resource drink from 4 hours following completion of operation. Regular diet for dinner if fluids tolerated and no nausea. Stop drinking if nausea or vomiting or hiccuping. Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)		
	Aim for placement in WARD 5E If morning surgery and patient returns to the ward prior to 1800 => sit out of bed		
Post Op Day 1 Date:	Continue Clexane 40mg sc until discharge (use 20mg if wt < 50kg or CrCl < 30) Continue TEDS until discharge		
	If IDC in consider removal after medical review. NB. Decision for removal will be based on the type of surgery.		
	Hourly breathing + coughing (I-COUGH resp bundle:		
	Antiemetics Ondansetron 4mg IV Q8h regular Maxolon 10mg IV Q8h regular: Do not use in patients > 75 years old.		
	Analgesia (see Appendix 1 for exclusions) Paracetamol 1g PO Q6h regular: Caution in patients < 60kg or with liver dysfunction. Pregabalin 75mg PO BD regular (50mg if > 70 yrs): Do not use if eGFR < 60. Coloxyl + Senna 1 tab BD, MgOH2 10ml BD (Fleet enema OD for right colectomy) Tramadol 50mg PO/subcut Q4h / PRN: Do not use if on SSRI or eGFR < 60. Avoid opioids completely if possible (contact surgical team if opioids required). If needed, then recommend half the age-based dosing and PCA as last resort. If PCA is required, stop pregabalin and refer to APS.		
	Oral intake General diet as tolerated. Fortijuce/Sustagen/Resource drink BD. Stop drinking if nausea or vomiting or hiccuping. Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)		
	Sit out of bed for meals 4 hours in chair during the day. May be split up.		
	60 metre walk (1st) 60 metre walk (2nd) **No bedpans or urinals.**		
Post Op Day 2 Date:	Potential for IDC removal after medical review		
	Hourly breathing + coughing (I-COUGH resp bundle: https://tinyurl.com/vctcw9x4)		
	Antiemetics Ondansetron 4mg PO / IV Q8h regular Maxolon 10mg PO / IV Q8h regular: Do not use in patients > 75 years old.		
	Analgesia (see Appendix 1 for exclusions) Paracetamol 1g PO Q6h regular: Caution in patients < 60kg or with liver dysfunction. Pregabalin 75mg PO BD regular (50mg if > 70 yrs): Do not use if eGFR < 60. Coloxyl + Senna 1 tab BD, MgOH2 10ml BD (Fleet enema OD for right colectomy) Tramadol 50mg PO/subcut Q4h / PRN: Do not use if on SSRI or eGFR < 60. Avoid opioids completely if possible (contact surgical team if opioids required). If needed, then recommend half the age-based dosing and PCA as last resort. If PCA is required, stop pregabalin and refer to APS.		
	Oral intake General diet as tolerated. Fortijuce/Sustagen/Resource drink BD. Stop drinking if nausea or vomiting or hiccuping. Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)		
	Sit out of bed for all meals 6 hours in chair during the day. Split up.		
	60 metres walk (1st) 60 metres walk (2nd) 60 metres walk (3rd) 60 metres walk (4th) **No bedpans or urinals.**		
	Order medications for discharge tomorrow		
	Hourly breathing + coughing (I-COUGH resp bundle:		
	Antiemetics Ondansetron 4mg PO / IV Q8h regular Maxolon 10mg PO / IV Q8h regular: Do not use in patients > 75 years old.		

Post op Day 3 Date:	**Analgesia (see Appendix 1 for exclusions) Consider change analgesia to prn** Paracetamol 1g PO Q6h regular: Caution in patients < 60kg or with liver dysfunction. Pregabalin 75mg PO BD regular (50mg if > 70 yrs): Do not use if eGFR < 60. Coloxyl + Senna 1 tab BD, MgOH2 10ml BD (Fleet enema OD for right colectomy) Tramadol 50mg PO/subcut Q4h / PRN: Do not use if on SSRI or eGFR < 60. Avoid opioids completely if possible (contact surgical team if opioids required). If needed, then recommend half the age-based dosing and PCA as last resort. If PCA is required, stop pregabalin and refer to APS.		
	Oral intake General diet as tolerated. Fortijuce/Sustagen/Resource drink BD. Stop drinking if nausea or vomiting or hiccuping. Early NG insertion if clinical suspicion of ileus (do not wait for vomiting)		
	Sit out of bed for all meals 8 hours in chair. Split up.		
	60 metre walk (1st) 60 metre walk (2nd) 60 metre walk (3rd) 60 metre walk (4th) 100 metre walk (1st) 100 metre walk (2nd)		
Post op Day 4 - Home Date:	Discharge patient if discharge criteria met. If not met, repeat instructions for Day 3. See 'Criteria for discharge' below.		
	100 metre walk (1st) 100 metre walk (2nd) 100 metre walk (3rd) 100 metre walk (4th) Can be discharged prior to completion of walks.		
	Oral analgesia / antiemetics take home.		
	Medical Staff please note criteria for safe		
Medical Staff Criteria for safe:	No clinical and biochemical concern		
	Tolerance of general diet		
	Passing flatus OR bowels opened.		
	Acceptable pain control on oral analgesia.		
	Mobilising independently.		
	If stoma present: patient managing care independently.		

Appendix 1: Some patient exclusions apply. Specifically, patients with significant renal impairment (eGFR < 60) or opioid tolerant.
(e.g. 60mg oral morphine/day, 40mg oxycodone/day, Fentanyl patch of 12mic/hr, or using illicit drugs).
All medications recommended should only be prescribed if no absoulte or relative contra-indication. This is the responsibility of the prescribing physican.
This a suggested guideline only, and may not apply to all patients. Individualised treatment is still required, including earlier discharge if clinically safe.
*https://www.uptodate.com/contents/intraoperative-fluid-management

Explanation of costs as provided by business intelligence and performance reporting unit, CALHN.

Cost	Definition
Medical staff	The cost of labour including salaries and wages for medical staff.
Nursing staff	The cost of labour including salaries and wages for nursing staff.
Allied health staff	The cost of labour including salaries and wages for allied health staff.
Indirect salary costs	Indirect salary costs including Superannuation, Termination Payments, Lump Sum Payments, Fringe Benefits Tax, Workers Compensation.
Critical care	Cost of services provided in an intensive care unit. For example, invasive life support, high levels of medical and nursing care and complex equipment.
Theatre	Costs for services provided where operative procedures are performed such as induction/anaesthesia, invasive and surgical operations and recovery.
Imaging	Imaging costs are goods and services used in the provision of an imaging service (including radiology imaging, contrast, etc.). This includes the cost of radiology staff.
Pathology	Pathology costs are goods and services used in the provision of a pathology service, consumables, and cost of staff.
Pharmacy	Goods and services used in the provision of a pharmaceutical service and consumables. This includes the purchase, production, distribution, supply and storage of drug products, clinical pharmacy services and cost of pharmacy staff.
Supplies	Medical and surgical supplies costs are goods and services used in the provision of surgical services.
Hospital services	Costs include cleaning products and services, linen and laundry services, food services (patients) and cost of hospital staff for these services.
Non-clinical	The cost of labour including salaries and wages for non-clinical staff.
Depreciation	Systematic allocation of the depreciable amount of an asset (building or equipment) over its useful life in line with Australian Accounting Standards. This involved building and equipment depreciation costs, such as light fittings and theatre tables.

CHEERS checklist

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	1
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	4
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	5
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	NA
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	6
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	6
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	6
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	NA
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	6
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	6
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	7. table 1,2,3,supleme
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	table 3
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	8

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	NA
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Table 2
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	8,9
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	In submission document
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

APPENDIX – D:

SUPPLEMENTARY MATERIAL FOR THE GLOBAL COST OF POSTOPERATIVE ILEUS FOLLOWING ABDOMINAL SURGERY: META-ANALYSIS.

Search strategy

Database	Search terms	Number of papers
Pubmed	("economics"[MeSH Terms] OR "economics"[All Fields] OR "financial"[All Fields] OR "financially"[All Fields] OR "financials"[All Fields] OR "financier"[All Fields] OR "financiers"[All Fields] OR ("economics"[MeSH Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR ("economical"[All Fields] OR "economics"[MeSH Terms] OR "economics"[All Fields] OR "economic"[All Fields] OR "economically"[All Fields] OR "economics"[MeSH Subheading] OR "economization"[All Fields] OR "economize"[All Fields] OR "economized"[All Fields] OR "economizes"[All Fields] OR "economizing"[All Fields]) OR ("commerce"[MeSH Terms] OR "commerce"[All Fields] OR "price"[All Fields] OR "prices"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields] OR "pricing"[All Fields] OR "priced"[All Fields] OR "pricings"[All Fields]) OR ("fiscal"[All Fields] OR "fiscally"[All Fields])) AND ("ileus"[MeSH Terms] OR "ileus"[All Fields]) AND ("abdom surg"[Journal] OR ("abdominal"[All Fields] AND "surgery"[All Fields]) OR "abdominal surgery"[All Fields])	160
CIANHL	AB (costs or cost or expense or affordability or financial burden or health care costs) AND AB (ileus or paralytic ileus or postoperative ileus) AND AB (abdominal surgery or surgery or postoperative or recovery)	99
Cochrane systematic review	((costs or cost or expense or affordability or financial burden or health care costs) and (ileus or paralytic ileus or postoperative ileus) and (abdominal surgery or surgery or postoperative or recovery)).af	101
Cochrane Central Register of Controlled Trials	(cost and ileus).af	164
Embase	((costs or cost or expense or affordability or financial burden or health care costs) and (ileus or paralytic ileus or postoperative ileus) and (abdominal surgery or surgery or postoperative or recovery)).ab.	753
Medline	AB (costs or cost or expense or affordability or financial burden) AND AB (ileus or paralytic ileus	389

	or postoperative ileus) AND AB (abdominal surgery or surgery or postoperative or recovery)	
Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily	((costs or cost or expense or affordability or financial burden or health care costs) and (ileus or paralytic ileus or postoperative ileus) and (abdominal surgery or surgery or postoperative or recovery)).ab	379
Clinicaltrials.gov	Cost and ileus	26

Definitions of POI of included studies

Reference	Definition of POI
Asgeirrson[127]	Primary POI - 3 episodes of emesis in 24 hours and return to NPO and/or insertion of an NG tube Secondary POI - associated with an intra-abdominal complication.
Gan[27]	ICD-9 Codes
Goldstein[28]	ICD-9 Codes
Iyer[29]	ICD-9 codes
Mao[126]	Defined by ≥2 of following criteria ≥ day 4 postop: -nausea or vomiting -intolerance of diet -abdominal distension -absence of flatus and stool -radiological evidence
Nutt[30]	ICD-9 Code
Peters[125]	POI - Not achieving flatus or stool passage and inability to tolerate a regular oral diet by day four. Late POI – experiencing symptoms of POI after day 4.
Salvador[31]	Documented in records, radiology, delayed return of gastrointestinal function
Traeger[261]	GI-2 (validated composite measure of time to first stool and tolerance of oral diet) not achieved by day 4.

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	p. 5, Table S1.
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	p. 5,6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	p. 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	p. 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 6

Topic	No.	Item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	p. 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	p. 6,7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	p. 6,7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 6,7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 6,7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 6,7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	p. 6,7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 6,7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	p. 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	p. 8, Fig 1.

Topic	No.	Item	Location where item is reported
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Fig 1.
Study characteristics	17	Cite each included study and present its characteristics.	p. 8, table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 9, table 4, Fig 2-3.
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	p. 8-10, Table 1-3, Figure 2-3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	p. 8-10. Fig 2-3.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p9-10, table 5,6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p9-10, table 5-6, figure 2-3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p9-10, table 5-6, figure 2-3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	p9-10, table 5-6, figure 2-3
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	p9-10, table 5-6, figure 2-3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p 11-13
	23b	Discuss any limitations of the evidence included in the review.	p. 12-13
	23c	Discuss any limitations of the review processes used.	p. 12-13
	23d	Discuss implications of the results for practice, policy, and future research.	p. 14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	p. 5

Topic	No.	Item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	p. 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N.A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	p. 1
Competing interests	26	Declare any competing interests of review authors.	p. 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Table 1-4.

PRIMSA ABSTRACT CHECKLIST

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			

Topic	No.	Item	Reported?
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

APPENDIX – E:

PYRICO-RCT – PYRIDOSTIGMINE TO REDUCE THE DURATION OF POSTOPERATIVE ILEUS AFTER COLORECTAL SURGERY – A DOUBLE BLINDED RANDOMISED CONTROLLED TRIAL.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3,4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5,6
	2b	Specific objectives or hypotheses	5,6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6,7
	4b	Settings and locations where the data were collected	6,7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7,8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	7,8
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	8
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	7
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9, Statistical analysis plan

	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	9, Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	9, Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	9
	14b	Why the trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9, Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9,10, table 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9,10, table 2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Supplement table 1
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	10-13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-13
Other information			
Registration	23	Registration number and name of trial registry	4
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org

Dissolution test

eurofins | Chemical Analysis

C2111200/1:	**Pyridostigmine 60 mg Capsules Batch: T959196**
C2111200/2:	**Pyridostigmine 60 mg Capsules Batch: T959219**

EXPERIMENTAL:

Sample 1 used for method development to confirm method:
Sample disintegration performed as per USPNF 2021 <701> in water with no discs. Sample shell disintegration time and content disintegration times recorded for 6 replicate samples.
C2111200/1 Capsule disintegration range: 1 min 15 secs to 2 min 31 secs, contents disintegration range: 8 min 26 sec to 11 min 05 secs.
Method determined as suitable for testing C2111200/2.

RESULTS:

C2111200/2:	**Pyridostigmine 60 mg Capsules Batch: T959219**		
Tests	**Specifications**	**Results**	**Complies/Not Complies/NA**
Disintegration	Record only	All capsules and contents disintegrated within 10 min 52 secs	NA

CONCLUSIONS:

Testing of Pyridostigmine 60 mg Capsules can be performed as per USPNF 2021 <701> method, using water and no discs for analysis.

Reviewed by: Elspeth Bowen, Chemistry Manager	Approved by: Wendy Musgrove, Senior Quality Associate

Statistical Analysis Plan

SAP Version: 1.1
SAP Date: 4 June 2023
SAP Author: Shalem Leemaqz

Approved by:

	Signature	***Date***
Luke Traeger		4th June 2023

Study Design
Double blind, randomised controlled trial.
Adult patients (over 18 years of age) who are undergoing elective large or small bowel resection, or undergoing reversal of Hartmann's or loop ileostomies or formation of stoma procedure, are randomised to the control group (standard care + placebo) or the intervention group (standard care + oral pyridostigmine). Study tablets (placebo/oral pyridostigmine) are given from 6h after operation until bowel action. A simple randomisation in 1:1 ratio to control and intervention was used, with no stratification variables.

Sample Size
To detect a clinically meaningful 1-day reduction in the mean duration of postoperative ileus between the treatment groups with 80% power, a sample size of 55 participants per group is required (based on a two-sample t-test with alpha=0.05 and SD=1.85 from the SIMULAX trial). A recruitment target of 65 participants per group was set to allow for withdrawals/loss to follow-up.

Analysis Approach
Outcomes (defined in Outcomes section below) will be compared between the control and intervention group using univariate analysis. For continuous outcomes, Student's *t*-test will be used and where test assumptions do not hold, Mann-Whitney U-test will be performed as a non-parametric alternative. For categorical outcomes, Chi-square test will be used, or Fisher's exact test when there are low expected cell counts. Kaplan-Meier curves will also be plotted for time-to-event outcomes, including the primary outcome (GI-2), time to flatus and time to first stool.
Analysis will be performed on complete-case data, with no adjustment for multiple testing.

Descriptive Statistics
Descriptive information for baseline patient data and operative characteristics will be provided on the following variables by intervention group.

Patient characteristics	**Details**	**Descriptive statistic**
Age, years	Continuous	Mean (SD) or median (IQR)
Gender	Male/Female	N (%)
ASA	1-3	N (%)
Smoker	Ex smoker/active/no	N (%)
BMI, kg/m^2	continuous	Mean (SD) or median (IQR)
Congestive cardiac failure in last 30 days	Yes/No	N (%)
Chronic obstructive pulmonary disease	Yes/No	N (%)
Hypertension	Yes/No	N (%)
Diabetes mellitus	Yes/No	N (%)
Regular Steroid use	Yes/No	N (%)
Preoperative Hb (g/L)	Continuous	Mean (SD) or median (IQR)
Preoperative albumin (g/L)	Continuous	Mean (SD) or median (IQR)
Previous abdominal surgery	Yes/No	N (%)
Malignancy	Yes/No	N (%)
Malignancy side	Left/right	N (%)

Operative characteristics	**Details**	**Descriptive statistic**
Surgical approach	Open/Laparoscopic	N (%)

Conversion from laparoscopic to open	Yes/No	N (%)
Primary operation	Anterior resection, APR/Hartmann's, Pelvic exenteration, right colectomy, formation of stoma, reversal of ileostomy, reversal of Hartmann's, pan/proctocolectomy, sub/total colectomy, small bowel resection	N (%)
Stoma performed	Yes/No	N (%)
Stoma type formed	Ileostomy/Colostomy/DBUC	N (%)
Epidural/spinal	Yes/No	N (%)
Neostigmine/Glycopyrrolate used in neuromuscular reversal	Yes/No	N (%)
Intraoperative/recovery opioids, MEQ	Continuous	Mean (SD) or median (IQR)
Theatre duration, min	Continuous	Mean (SD) or median (IQR)
TAP Catheter/Block	Yes/No	N (%)
Intraoperative complications	Yes/No	N (%)
Intraoperative intravenous fluids used, ml	Continuous	Mean (SD) or median (IQR)
Recovery intravenous fluids used, ml	Continuous	Mean (SD) or median (IQR)
Patient Controlled anaesthesia	Yes/No	N (%)

Outcomes

Univariate analysis will be performed for the following outcomes.

Primary outcome	**Details**	**Analysis**
GI-2, days	Continuous	*t*-test or Mann-Whitney U-test, Kaplan-Meier curves

Secondary outcomes	**Details**	**Analysis**
Prolonged POI (GI-2 > 4 days)	Yes/No	Chi-square or Fisher's exact test
Time to first flatus, days	Continuous	*t*-test or Mann-Whitney U-test, Kaplan-Meier curves
Time to first stool, days	Continuous	*t*-test or Mann-Whitney U-test, Kaplan-Meier curves
Bristol stool type	Continuous	*t*-test or Mann-Whitney U-test
Time to tolerance of oral diet, days	Continuous	*t*-test or Mann-Whitney U-test
Required TPN	Yes/No	Chi-square or Fisher's exact test
Number of days with TPN	Continuous	*t*-test or Mann-Whitney U-test
NGT reinserted	Yes/No	Chi-square or Fisher's exact test
Number of days with NGT	Continuous	*t*-test or Mann-Whitney U-test
Nausea	Yes/No	Chi-square or Fisher's exact test
Vomiting	Yes/No	Chi-square or Fisher's exact test
Postoperative opioid use (Day 1-4), MEQ	Continuous	*t*-test or Mann-Whitney U-test
Daily average pain score (at rest)	Continuous	*t*-test or Mann-Whitney U-test
Daily average pain score (on activity)	Continuous	*t*-test or Mann-Whitney U-test
Maximum pain score	Continuous	*t*-test or Mann-Whitney U-test
Lowest postoperative potassium, mmol/L	Continuous	t-test or Mann-Whitney U-test
ARC/CCU admission	Yes/No	Chi-square or Fisher's exact test
ICU admission	Yes/No	Chi-square or Fisher's exact test
Return to theatre	Yes/No	Chi-square or Fisher's exact test
Readmission	Yes/No	Chi-square or Fisher's exact test
Length of Stay, days	Continuous	*t*-test or Mann-Whitney U-test
Complication	Yes/No	Chi-square or Fisher's exact test
30-day postoperative complications (Highest Clavien-dindo)	1/2/3/4/5	Chi-square or Fisher's exact test
30-day postoperative complications (Comprehensive complications index)	Continuous	*t*-test or Mann-Whitney U-test
Direct Hospital cost ($)	Continuous	*t*-test or Mann-Whitney U-test

Specific Complications	Details	Analysis
Anastomotic leak	Yes/No	Chi-square or Fisher's exact test
Wound infection	Yes/No	Chi-square or Fisher's exact test
Other infection	Yes/No	Chi-square or Fisher's exact test
Transfusion	Yes/no	Chi-square or Fisher's exact test
SBO/Pseudo obstruction	Yes/no	Chi-square or Fisher's exact test
Urinary retention	Yes/No	Chi-square or Fisher's exact test
Neurological	Yes/No	Chi-square or Fisher's exact test
Respiratory	Yes/No	Chi-square or Fisher's exact test
Hypotension	Yes/No	Chi-square or Fisher's exact test
Diarrhea/HOS	Yes/No	Chi-square or Fisher's exact test
Electrolytes	Yes/No	Chi-square or Fisher's exact test
Cardiac complication	Yes/No	Chi-square or Fisher's exact test
AKI	Yes/No	Chi-square or Fisher's exact test
VTE	Yes/No	Chi-square or Fisher's exact test
Bleeding requiring transfusion	Yes/No	Chi-square or Fisher's exact test

Patient reported outcomes	Details	Analysis
Do you agree this medication assisted with opening your bowel following your operation	Strongly Disagree/Disagree/Neither/Agree/Strongly agree	Chi-square or Fisher's exact test
How satisfied or unsatisfied are you with the way the medication relieved your constipation?	Strongly Disagree/Disagree/Neither/Agree/Strongly agree	Chi-square or Fisher's exact test
How satisfied or unsatisfied are you with the amount of time it takes the medication to start working?	Strongly Disagree/Disagree/Neither/Agree/Strongly agree	Chi-square or Fisher's exact test
As a result of this medication, did you experience any side effects at all?	Yes/No	Chi-square or Fisher's exact test
How bothersome where the side effects	Not bothersome/ somewhat bothersome /Neither/Bothersome/Very bothersome	Chi-square or Fisher's exact test
Reported side effects	Diarrhea/Dry mouth/muscle twitching/Sweating/Nausea/Vomiting/	Chi-square or Fisher's exact test
How easy or difficult is it to use the medication in its current form?	Very inconvenient / inconvenient /Neither/convenient/ Very convenient	Chi-square or Fisher's exact test
How convenient or inconvenient is it to take the medication as instructed?	Very inconvenient / inconvenient /Neither/convenient/ Very convenient	Chi-square or Fisher's exact test
Taking all things into account, how satisfied or unsatisfied are you with this medication?	Very unsatisfied / unsatisfied /Neither/satisfied/ Very satisfied	Chi-square or Fisher's exact test

APPENDIX – F:

SUPPLEMENTARY MATERIAL FOR MACHINE LEARNING PREDICTION MODEL FOR POSTOPERATIVE ILEUS FOLLOWING COLORECTAL SURGERY

TRIPOD Checklist

Section/Topic		Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2,3
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	4,5
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	4,5
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6,7
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	Describe eligibility criteria for participants.	6
	5c	Give details of treatments received, if relevant.	6,7
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6,7
	6b	Report any actions to blind assessment of the outcome to be predicted.	NA
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6,7
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	NA
Sample size	8	Explain how the study size was arrived at.	NA
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	8
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7,8
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7,8
Risk groups	11	Provide details on how risk groups were created, if done.	NA
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	9, Figure 1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	9 Table 1
Model development	14a	Specify the number of participants and outcome events in each analysis.	9,10
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	9,10
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	9,10, Table 3, Figure 2
	15b	Explain how to the use the prediction model.	Appendix
Model performance	16	Report performance measures (with CIs) for the prediction model.	10, Table 3, Figure 2
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	13,14
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	11-14
Implications	20	Discuss the potential clinical use of the model and implications for future research.	11-14
Other information			

Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Appendix
Funding	22	Give the source of funding and the role of the funders for the present study.	16

Table 1. Cut-offs used for binary outcome for prediction models.

Variable	Yes	No	Rationale/explanation
Age, years	>65 years old	<65 years old	Median age of cohort
Sex	Male	Female	
BMI, kg/m^2	≥30	<30	Obesity if >30 kg/m^2
ASA	3-4	1-2	ASA >2 considered high
Dependence	Yes	No	Dependence on others is indicative of frailty
Sarcopenia	Yes	No	Sarcopenia is another measure of frailty
Smoking history	Yes	No	Associated with poor postoperative outcomes
Diabetes Mellitus	Yes	No	Associated with poor postoperative outcomes
Congestive cardiac failure	Yes	No	Associated with poor postoperative outcomes
Chronic obstructive pulmonary disease	Yes	No	Associated with poor postoperative outcomes
Hypertension	Yes	No	Associated with poor postoperative outcomes
Regular steroid use	Yes	No	Associated with poor postoperative outcomes
Previous abdominal surgery	Yes	No	Associated with prolonged theatre duration and increased adhesions
Malignancy	Yes	No	Comparison between
Preoperative Haemoglobin, g/dl	<110	≥110	<110 g/dL is the cut-off for anaemia in our institution
Preoperative Total Protein, g/L	<60	≥60	<60 g/dL is the cut-off for total protein in our institution
Preoperative Albumin, g/L	<34	≥34	<34 g/dL is the cut-off for hypoalbuminemia in our institution
Surgical Approach	Laparoscopic	Open	Laparoscopic approach associated with decreased incidence of POI
Conversion from to open	Yes	No	Associated with poor postoperative outcomes
Left sided resection	Yes	No	Associated with poor postoperative outcomes
Stoma	Yes	No	
Operative time, min	>180	≤180	Median operative time of cohort
Neostigmine in Neuromuscular reversal	Yes	No	Associated with delayed return of GI function
Intraoperative opioids, MEQ	>150	≤150	Median opioid use of cohort
Postoperative opioids, MEQ	>162	≤162	Median opioid use of cohort
Postoperative Potassium, mmol/l	<3.5	≥3.5	<3.5 mmol/L is the cut-off for hypokalamiea in our institution
Intraoperative fluids, ml	>2000	≤2000	Median intravenous fluid use of cohort
Postoperative fluids, ml	>1000	≤1000	Median intravenous fluid use of cohort
Blood transfusion required	Yes	No	Associated with poor postoperative outcomes
Intensive care unit admission	Yes	No	Associated with poor postoperative outcomes

LIST OF REFERENCES

[1] Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS(R)) Society Recommendations: 2018. *World J Surg*. 2019; 43:659-95.

[2] Munoz E, Munoz W, Wise L. National and surgical health care expenditures, 2005-2025. *Ann Surg*. 2010; 251:195-200.

[3] Tevis SE, Carchman EH, Foley EF, Harms BA, Heise CP, Kennedy GD. Postoperative Ileus--More than Just Prolonged Length of Stay? *J Gastrointest Surg*. 2015; 19:1684-90.

[4] Vather R, Trivedi S, Bissett I. Defining postoperative ileus: results of a systematic review and global survey. *J Gastrointest Surg*. 2013; 17:962-72.

[5] Tebala GD. History of colorectal surgery: A comprehensive historical review from the ancient Egyptians to the surgical robot. *Int J Colorectal Dis*. 2015; 30:723-48.

[6] Australian Institute of Health and Welfare. *Elective surgery activity*. AIHW, [updated 11/08/2023; cited 2023].Available from: https://www.aihw.gov.au/reports-data/myhospitals/intersection/activity/eswt

[7] Ehsani JP, Jackson T, Duckett SJ. The incidence and cost of adverse events in Victorian hospitals 2003-04. *Med J Aust*. 2006; 184:551-5.

[8] Kirchhoff P, Clavien PA, Hahnloser D. Complications in colorectal surgery: risk factors and preventive strategies. *Patient Saf Surg*. 2010; 4:5.

[9] Viannay P, Hamel JF, Bougard M, Barbieux J, Hamy A, Venara A. Gastrointestinal motility has more of an impact on postoperative recovery than you might expect. *J Visc Surg*. 2021; 158:19-26.

[10] Wattchow D, Heitmann P, Smolilo D, et al. Postoperative ileus-An ongoing conundrum. *Neurogastroenterol Motil*. 2021; 33:e14046.

[11] Okamoto A, Kohama K, Aoyama-Ishikawa M, et al. Intraperitoneally administered, hydrogen-rich physiologic solution protects against postoperative ileus and is associated with reduced nitric oxide production. *Surgery*. 2016; 160:623-31.

[12] Scarborough JE, Schumacher J, Kent KC, Heise CP, Greenberg CC. Associations of Specific Postoperative Complications With Outcomes After Elective Colon Resection: A Procedure-Targeted Approach Toward Surgical Quality Improvement. *JAMA Surg*. 2017; 152:e164681.

[13] Li ZL, Zhao BC, Deng WT, et al. Incidence and risk factors of postoperative ileus after hysterectomy for benign indications. *Int J Colorectal Dis*. 2020; 35:2105-12.

[14] Chapuis PH, Bokey L, Keshava A, et al. Risk factors for prolonged ileus after resection of colorectal cancer: an observational study of 2400 consecutive patients. *Ann Surg*. 2013; 257:909-15.

[15] Chapman SJ, Thorpe G, Vallance AE, et al. Systematic review of definitions and outcome measures for return of bowel function after gastrointestinal surgery. *BJS Open*. 2019; 3:1-10.

[16] Venara A, Neunlist M, Slim K, et al. Postoperative ileus: Pathophysiology, incidence, and prevention. *J Visc Surg*. 2016; 153:439-46.

[17] Wolthuis AM, Bislenghi G, Fieuws S, de Buck van Overstraeten A, Boeckxstaens G, D'Hoore A. Incidence of prolonged postoperative ileus after colorectal surgery: a systematic review and meta-analysis. *Colorectal Dis*. 2016; 18:O1-9.

[18] Reed LA, Mihas AK, Fortin TA, et al. Risk Factors for Postoperative Ileus After Thoracolumbar and Lumbar Spinal Fusion Surgery: Systematic Review and Meta-Analysis. *World Neurosurg*. 2022; 168:e381-e92.

[19] Wells CI, Milne TGE, Seo SHB, et al. Post-operative ileus: definitions, mechanisms and controversies. *ANZ J Surg*. 2022; 92:62-8.

[20] Stakenborg N, Gomez-Pinilla PJ, Boeckxstaens GE. Postoperative Ileus: Pathophysiology, Current Therapeutic Approaches. *Handb Exp Pharmacol*. 2017; 239:39-57.

[21] Gero D, Gié O, Hübner M, Demartines N, Hahnloser D. Postoperative ileus: in search of an international consensus on definition, diagnosis, and treatment. *Langenbecks Arch Surg*. 2017; 402:149-58.

[22] Peters EG, Dekkers M, van Leeuwen-Hilbers FW, et al. Relation between postoperative ileus and anastomotic leakage after colorectal resection: a post hoc analysis of a prospective randomized controlled trial. *Colorectal Dis*. 2017; 19:667-74.

[23] Venara A, Alfonsi P, Cotte E, et al. Postoperative ileus concealing intra-abdominal complications in enhanced recovery programs-a retrospective analysis of the GRACE database. *Int J Colorectal Dis*. 2019; 34:71-83.

[24] Chapman SJ, Wells CI. Challenges in ileus research. *Colorectal Dis*. 2018; 20:639.

[25] van Bree SH, Bemelman WA, Hollmann MW, et al. Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus. *Ann Surg*. 2014; 259:708-14.

[26] Read TE, Brozovich M, Andujar JE, Ricciardi R, Caushaj PF. Bowel Sounds Are Not Associated With Flatus, Bowel Movement, or Tolerance of Oral Intake in Patients After Major Abdominal Surgery. *Dis Colon Rectum*. 2017; 60:608-13.

[27] Gan TJ, Robinson SB, Oderda GM, Scranton R, Pepin J, Ramamoorthy S. Impact of postsurgical opioid use and ileus on economic outcomes in gastrointestinal surgeries. *Curr Med Res Opin*. 2015; 31:677-86.

[28] Goldstein JL, Matuszewski KA, Delaney CP, et al. Inpatient economic burden of postoperative ileus associated with abdominal surgery in the United States. *P&T*. 2007; 32:82-90.

[29] Iyer S, Saunders WB, Stemkowski S. Economic burden of postoperative ileus associated with colectomy in the United States. *J Manag Care Pharm*. 2009; 15:485-94.

[30] Nutt M, Scaief S, Dynda D, Alanee S. Ileus and small bowel obstruction after radical cystectomy for bladder cancer: Analysis from the Nationwide Inpatient Sample. *Surg Oncol*. 2018; 27:341-5.

[31] Salvador CG, Sikirica M, Evans A, Pizzi L, Goldfarb N. Clinical and economic outcomes of prolonged postoperative ileus in patients undergoing hysterectomy and hemicolectomy. *P&T*. 2005; 30:590.

[32] Cromwell JW, Lund LW. Hospital Coding of Postoperative Ileus: A Prospective Study. *Cureus*. 2022; 14:e24946.

[33] Tripartite Gastrointestinal Recovery Post-operative Ileus Group. Core outcome set for clinical studies of postoperative ileus after intestinal surgery. *Br J Surg*. 2022; 109:493-6.

[34] Vather R, O'Grady G, Bissett IP, Dinning PG. Postoperative ileus: mechanisms and future directions for research. *Clin Exp Pharmacol Physiol*. 2014; 41:358-70.

[35] Buscail E, Deraison C. Postoperative ileus: A pharmacological perspective. *Br J Pharmacol*. 2022; 179:3283-305.

[36] Gershon MD, Margolis KG. The gut, its microbiome, and the brain: connections and communications. *J Clin Invest*. 2021; 131:e143768.

[37] Spencer NJ, Hu H. Enteric nervous system: sensory transduction, neural circuits and gastrointestinal motility. *Nat Rev Gastroenterol Hepatol*. 2020; 17:338-51.

[38] Harrington AM, Caraballo SG, Maddern JE, Grundy L, Castro J, Brierley SM. Colonic afferent input and dorsal horn neuron activation differs between the thoracolumbar and lumbosacral spinal cord. *Am J Physiol Gastrointest Liver Physiol*. 2019; 317:G285-G303.

[39] Wood JD. Neurotransmission at the interface of sympathetic and enteric divisions of the autonomic nervous system. *Chin J Physiol*. 1999; 42:201-10.

[40] Lomax AE, Sharkey KA, Furness JB. The participation of the sympathetic innervation of the gastrointestinal tract in disease states. *Neurogastroenterol Motil*. 2010; 22:7-18.

[41] Osadchiy V, Martin CR, Mayer EA. Gut Microbiome and Modulation of CNS Function. *Compr Physiol*. 2019; 10:57-72.

[42] Berthoud HR, Neuhuber WL. Functional and chemical anatomy of the afferent vagal system. *Auton Neurosci*. 2000; 85:1-17.

[43] Takaki M. Gut pacemaker cells: the interstitial cells of Cajal (ICC). *J Smooth Muscle Res*. 2003; 39:137-61.

[44] McMinn RMH. *Last's Anatomy: Regional and Applied*. 9th ed: Churchill Livingstone, 2009.

[45] Boeckxstaens GE, de Jonge WJ. Neuroimmune mechanisms in postoperative ileus. *Gut*. 2009; 58:1300-11.

[46] Furness JB. *The enteric nervous system*. 1st ed: Oxford: Blackwell Publishing, 2006.

[47] Stoffels B, Hupa KJ, Snoek SA, et al. Postoperative ileus involves interleukin-1 receptor signaling in enteric glia. *Gastroenterology*. 2014; 146:176-87 e1.

[48] de Jonge WJ, van den Wijngaard RM, The FO, et al. Postoperative ileus is maintained by intestinal immune infiltrates that activate inhibitory neural pathways in mice. *Gastroenterology*. 2003; 125:1137-47.

[49] Thayer JF, Sternberg EM. Neural aspects of immunomodulation: focus on the vagus nerve. *Brain Behav Immun*. 2010; 24:1223-8.

[50] Sanders KM, Koh SD, Ro S, Ward SM. Regulation of gastrointestinal motility--insights from smooth muscle biology. *Nat Rev Gastroenterol Hepatol*. 2012; 9:633-45.

[51] Boeckxstaens GE, Hirsch DP, Kodde A, et al. Activation of an adrenergic and vagally-mediated NANC pathway in surgery-induced fundic relaxation in the rat. *Neurogastroenterol Motil*. 1999; 11:467-74.

[52] Takahashi T, Owyang C. Vagal control of nitric oxide and vasoactive intestinal polypeptide release in the regulation of gastric relaxation in rat. *J Physiol*. 1995; 484:481-92.

[53] Yokotani K, Okuma Y, Nakamura K, Osumi Y. Release of endogenous acetylcholine from a vascularly perfused rat stomach in vitro; inhibition by M3 muscarinic autoreceptors and alpha-2 adrenoceptors. *J Pharmacol Exp Ther*. 1993; 266:1190-5.

[54] Langer SZ. 25 years since the discovery of presynaptic receptors: present knowledge and future perspectives. *Trends Pharmacol Sci*. 1997; 18:95-9.

[55] Fuder H, Muscholl E. Heteroreceptor-mediated modulation of noradrenaline and acetylcholine release from peripheral nerves. *Rev Physiol Biochem Pharmacol*. 1995; 126:265-412.

[56] Kalff JC, Turler A, Schwarz NT, et al. Intra-abdominal activation of a local inflammatory response within the human muscularis externa during laparotomy. *Ann Surg*. 2003; 237:301-15.

[57] The FO, Bennink RJ, Ankum WM, et al. Intestinal handling-induced mast cell activation and inflammation in human postoperative ileus. *Gut*. 2008; 57:33-40.

[58] Kreiss C, Birder LA, Kiss S, VanBibber MM, Bauer AJ. COX-2 dependent inflammation increases spinal Fos expression during rodent postoperative ileus. *Gut*. 2003; 52:527-34.

[59] Echtenacher B, Mannel DN, Hultner L. Critical protective role of mast cells in a model of acute septic peritonitis. *Nature*. 1996; 381:75-7.

[60] de Jonge WJ, The FO, van der Coelen D, et al. Mast cell degranulation during abdominal surgery initiates postoperative ileus in mice. *Gastroenterology*. 2004; 127:535-45.

[61] Kalff JC, Carlos TM, Schraut WH, Billiar TR, Simmons RL, Bauer AJ. Surgically induced leukocytic infiltrates within the rat intestinal muscularis mediate postoperative ileus. *Gastroenterology*. 1999; 117:378-87.

[62] Barbara G, Wang B, Stanghellini V, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology*. 2007; 132:26-37.

[63] Millan M, Biondo S, Fraccalvieri D, Frago R, Golda T, Kreisler E. Risk factors for prolonged postoperative ileus after colorectal cancer surgery. *World J Surg*. 2012; 36:179-85.

[64] Viola MF, Boeckxstaens G. Intestinal resident macrophages: Multitaskers of the gut. *Neurogastroenterol Motil*. 2020; 32:e13843.

[65] Kalff JC, Schraut WH, Billiar TR, Simmons RL, Bauer AJ. Role of inducible nitric oxide synthase in postoperative intestinal smooth muscle dysfunction in rodents. *Gastroenterology*. 2000; 118:316-27.

[66] Schwarz NT, Kalff JC, Turler A, et al. Prostanoid production via COX-2 as a causative mechanism of rodent postoperative ileus. *Gastroenterology*. 2001; 121:1354-71.

[67] Shah SK, Uray KS, Stewart RH, Laine GA, Cox CS, Jr. Resuscitation-induced intestinal edema and related dysfunction: state of the science. *J Surg Res*. 2011; 166:120-30.

[68] Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet*. 2002; 359:1812-8.

[69] De Backer O, Elinck E, Blanckaert B, Leybaert L, Motterlini R, Lefebvre RA. Water-soluble CO-releasing molecules reduce the development of postoperative ileus via modulation of MAPK/HO-1 signalling and reduction of oxidative stress. *Gut*. 2009; 58:347-56.

[70] Chowdhury AH, Lobo DN. Fluids and gastrointestinal function. *Curr Opin Clin Nutr Metab Care*. 2011; 14:469-76.

[71] Sanger GJ, Furness JB. Ghrelin and motilin receptors as drug targets for gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol*. 2016; 13:38-48.

[72] Goetz B, Benhaqi P, Glatzle J, et al. Changes in peptidergic neurotransmission during postoperative ileus in rat circular jejunal muscle. *Neurogastroenterol Motil*. 2014; 26:397-409.

[73] Nightingale J, Spiller R. Intestinal Failure. In: Nightingale J, (ed) *Normal Intestinal Anatomy and Physiology*. Switzerland: Spinger Nature, 2023; 13-30.

[74] Chandrasekharan B, Nezami BG, Srinivasan S. Emerging neuropeptide targets in inflammation: NPY and VIP. *Am J Physiol Gastrointest Liver Physiol*. 2013; 304:G949-57.

[75] Delgado M, Ganea D. Inhibition of endotoxin-induced macrophage chemokine production by VIP and PACAP in vitro and in vivo. *Arch Physiol Biochem*. 2001; 109:377-82.

[76] Margolis KG, Gershon MD. Neuropeptides and inflammatory bowel disease. *Curr Opin Gastroenterol*. 2009; 25:503-11.

[77] Simpson J, Sundler F, Humes DJ, Jenkins D, Scholefield JH, Spiller RC. Post inflammatory damage to the enteric nervous system in diverticular disease and its relationship to symptoms. *Neurogastroenterol Motil*. 2009; 21:847-e58.

[78] Bissett IP, Lobo DN. Intestinal Failure. In: Nightingale J, (ed) *Postoperative Ileus*. Switzerland: Spinger Nature, 2023; 43-52.

[79] Kraichely RE, Farrugia G. Mechanosensitive ion channels in interstitial cells of Cajal and smooth muscle of the gastrointestinal tract. *Neurogastroenterol Motil*. 2007; 19:245-52.

[80] Kaji N, Nakayama S, Horiguchi K, Iino S, Ozaki H, Hori M. Disruption of the pacemaker activity of interstitial cells of Cajal via nitric oxide contributes to postoperative ileus. *Neurogastroenterol Motil*. 2018.

[81] Kito Y, Ward SM, Sanders KM. Pacemaker potentials generated by interstitial cells of Cajal in the murine intestine. *Am J Physiol Cell Physiol*. 2005; 288:C710-20.

[82] Ward SM, Beckett EA, Wang X, Baker F, Khoyi M, Sanders KM. Interstitial cells of Cajal mediate cholinergic neurotransmission from enteric motor neurons. *J Neurosci*. 2000; 20:1393-403.

[83] Kronberg U, Kiran RP, Soliman MS, et al. A characterization of factors determining postoperative ileus after laparoscopic colectomy enables the generation of a novel predictive score. *Ann Surg*. 2011; 253:78-81.

[84] Vather R, Josephson R, Jaung R, Robertson J, Bissett I. Development of a risk stratification system for the occurrence of prolonged postoperative ileus after colorectal surgery: a prospective risk factor analysis. *Surgery*. 2015; 157:764-73.

[85] Fearon KC, Ljungqvist O, Von Meyenfeldt M, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr*. 2005; 24:466-77.

[86] Wind J, Polle SW, Fung Kon Jin PH, et al. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg*. 2006; 93:800-9.

[87] Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. *Clin Nutr*. 2010; 29:434-40.

[88] Abraham-Nordling M, Hjern F, Pollack J, Prytz M, Borg T, Kressner U. Randomized clinical trial of fluid restriction in colorectal surgery. *Br J Surg*. 2012; 99:186-91.

[89] Delaney CP. Clinical perspective on postoperative ileus and the effect of opiates. *Neurogastroenterol Motil*. 2004; 16 Suppl 2:61-6.

[90] Lin AY, Dinning PG, Milne T, Bissett IP, O'Grady G. The "rectosigmoid brake": Review of an emerging neuromodulation target for colorectal functional disorders. *Clin Exp Pharmacol Physiol*. 2017; 44:719-28.

[91] Vather R, O'Grady G, Lin AY, et al. Hyperactive cyclic motor activity in the distal colon after colonic surgery as defined by high-resolution colonic manometry. *Br J Surg*. 2018; 105:907-17.

[92] Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, deCarle D, Cook IJ. Spatial and temporal organization of pressure patterns throughout the unprepared colon during spontaneous defecation. *Am J Gastroenterol*. 2000; 95:1027-35.

[93] Dinning PG, Hunt LM, Arkwright JW, et al. Pancolonic motor response to subsensory and suprasensory sacral nerve stimulation in patients with slow-transit constipation. *Br J Surg*. 2012; 99:1002-10.

[94] Dinning PG, Zarate N, Hunt LM, et al. Pancolonic spatiotemporal mapping reveals regional deficiencies in, and disorganization of colonic propagating pressure waves in severe constipation. *Neurogastroenterol Motil*. 2010; 22:e340-9.

[95] Soffer EE, Scalabrini P, Wingate DL. Prolonged ambulant monitoring of human colonic motility. *Am J Physiol*. 1989; 257:G601-6.

[96] Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. Prolonged multi-point recording of colonic manometry in the unprepared human colon: providing insight into potentially relevant pressure wave parameters. *Am J Gastroenterol*. 2001; 96:1838-48.

[97] Lin Z, Yang C, Wang Y, Yan M, Zheng H. Comparison of prolonged postoperative ileus between laparoscopic right and left colectomy under enhanced recovery after surgery: a propensity score matching analysis. *World J Surg Oncol*. 2022; 20:68.

[98] Yuan L, O'Grady G, Milne T, Jaung R, Vather R, Bissett IP. Prospective comparison of return of bowel function after left versus right colectomy. *ANZ J Surg*. 2018; 88:E242-E7.

[99] Vather R, O'Grady G, Arkwright JW, et al. Restoration of normal colonic motor patterns and meal responses after distal colorectal resection. *Br J Surg*. 2016; 103:451-61.

[100] Alhashemi M, Fiore JF, Jr., Safa N, et al. Incidence and predictors of prolonged postoperative ileus after colorectal surgery in the context of an enhanced recovery pathway. *Surg Endosc*. 2019; 33:2313-22.

[101] Quiroga-Centeno AC, Jerez-Torra KA, Martin-Mojica PA, et al. Risk Factors for Prolonged Postoperative Ileus in Colorectal Surgery: A Systematic Review and Meta-analysis. *World J Surg*. 2020; 44:1612-26.

[102] Wolthuis AM, Bislenghi G, Lambrecht M, et al. Preoperative risk factors for prolonged postoperative ileus after colorectal resection. *Int J Colorectal Dis*. 2017; 32:883-90.

[103] Bauer AJ, Boeckxstaens GE. Mechanisms of postoperative ileus. *Neurogastroenterol Motil*. 2004; 16 Suppl 2:54-60.

[104] Artinyan A, Nunoo-Mensah JW, Balasubramaniam S, et al. Prolonged postoperative ileus-definition, risk factors, and predictors after surgery. *World J Surg*. 2008; 32:1495-500.

[105] Song X, Liu X, Liu F, Wang C. Comparison of machine learning and logistic regression models in predicting acute kidney injury: A systematic review and meta-analysis. *Int J Med Inform*. 2021; 151:104484.

[106] Cole J, Hughey S, Metzger A, Geiger P, Fluke L, Booth GJ. Machine Learning to Predict Fascial Dehiscence after Exploratory Laparotomy Surgery. *J Surg Res*. 2021; 268:514-20.

[107] Fernandes MPB, Armengol de la Hoz M, Rangasamy V, Subramaniam B. Machine Learning Models with Preoperative Risk Factors and Intraoperative Hypotension Parameters Predict Mortality After Cardiac Surgery. *J Cardiothorac Vasc Anesth*. 2021; 35:857-65.

[108] Li Y, Chen M, Lv H, Yin P, Zhang L, Tang P. A novel machine-learning algorithm for predicting mortality risk after hip fracture surgery. *Injury*. 2021; 52:1487-93.

[109] Bektas M, Tuynman JB, Costa Pereira J, Burchell GL, van der Peet DL. Machine Learning Algorithms for Predicting Surgical Outcomes after Colorectal Surgery: A Systematic Review. *World J Surg*. 2022; 46:3100-10.

[110] Spinelli A, Carrano FM, Laino ME, et al. Artificial intelligence in colorectal surgery: an AI-powered systematic review. *Tech Coloproctol*. 2023; 27:615-29.

[111] Li X, Genshan M, Qian X, Wu Y, Huang X, Gu C. Machine learning models for prediction of postoperative ileus in patients underwent laparoscopic colorectal surgery. Preprint, 2019.

[112] Weller GB, Lovely J, Larson DW, Earnshaw BA, Huebner M. Leveraging electronic health records for predictive modeling of post-surgical complications. *Stat Methods Med Res*. 2018; 27:3271-85.

[113] Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005; 242:326-41; discussion 41-3.

[114] Behm B, Stollman N. Postoperative ileus: etiologies and interventions. *Clin Gastroenterol Hepatol*. 2003; 1:71-80.

[115] Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. *Am J Health Syst Pharm*. 2007; 64:S3-7.

[116] Madl C, Druml W. Gastrointestinal disorders of the critically ill. Systemic consequences of ileus. *Best Pract Res Clin Gastroenterol*. 2003; 17:445-56.

[117] Yorkshire Surgical Research C. Multicentre observational study of gastrointestinal recovery after elective colorectal surgery. *Colorectal Dis*. 2018; 20:536-44.

[118] Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. *Cochrane Database Syst Rev*. 2007; 2007:CD004929.

[119] Sparn MB, Widmann B, Pietsch U, Weitzendorfer M, Warschkow R, Steffen T. Risk factors and outcomes of postoperative aspiration pneumonia in abdominal surgery patients: An exact matching and weighting analysis. *Surgery*. 2021; 170:1432-41.

[120] Lassen K, Soop M, Nygren J, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg*. 2009; 144:961-9.

[121] Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U. Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. *JAMA*. 2001; 286:944-53.

[122] Pile JC. Evaluating postoperative fever: a focused approach. *Cleve Clin J Med*. 2006; 73 Suppl 1:S62-6.

[123] Kehlet H, Holte K. Review of postoperative ileus. *Am J Surg*. 2001; 182:3S-10S.

[124] Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. *Ann Surg*. 2014; 259:916-23.

[125] Peters EG, Pattamatta M, Smeets BJJ, et al. The clinical and economical impact of postoperative ileus in patients undergoing colorectal surgery. *Neurogastroenterol Motil*. 2020; 32:e13862.

[126] Mao H, Milne TGE, O'Grady G, Vather R, Edlin R, Bissett I. Prolonged Postoperative Ileus Significantly Increases the Cost of Inpatient Stay for Patients Undergoing Elective Colorectal Surgery: Results of a Multivariate Analysis of Prospective Data at a Single Institution. *Dis Colon Rectum*. 2019; 62:631-7.

[127] Asgeirsson T, El-Badawi KI, Mahmood A, Barletta J, Luchtefeld M, Senagore AJ. Postoperative ileus: it costs more than you expect. *J Am Coll Surg*. 2010; 210:228-31.

[128] Vather R, Bissett I. Management of prolonged post-operative ileus: evidence-based recommendations. *ANZ J Surg*. 2013; 83:319-24.

[129] Vonlanthen R, Slankamenac K, Breitenstein S, et al. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. *Ann Surg*. 2011; 254:907-13.

[130] Delaney CP, Marcello PW, Sonoda T, Wise P, Bauer J, Techner L. Gastrointestinal recovery after laparoscopic colectomy: results of a prospective, observational, multicenter study. *Surg Endosc*. 2010; 24:653-61.

[131] Vignali A, Bissolati M, De Nardi P, Di Palo S, Staudacher C. Extracorporeal vs. Intracorporeal Ileocolic Stapled Anastomoses in Laparoscopic Right Colectomy: An Interim Analysis of a Randomized Clinical Trial. *J Laparoendosc Adv Surg Tech A*. 2016; 26:343-8.

[132] Hong X, Mistraletti G, Zandi S, Stein B, Charlebois P, Carli F. Laparoscopy for colectomy accelerates restoration of bowel function when using patient controlled analgesia. *Can J Anaesth*. 2006; 53:544-50.

[133] van Bree SH, Vlug MS, Bemelman WA, et al. Faster recovery of gastrointestinal transit after laparoscopy and fast-track care in patients undergoing colonic surgery. *Gastroenterology*. 2011; 141:872-80 e1-4.

[134] Marret E, Remy C, Bonnet F, Postoperative Pain Forum G. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *Br J Surg*. 2007; 94:665-73.

[135] Kuruba R, Fayard N, Snyder D. Epidural analgesia and laparoscopic technique do not reduce incidence of prolonged ileus in elective colon resections. *Am J Surg*. 2012; 204:613-8.

[136] Guay J, Nishimori M, Kopp S. Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, vomiting and pain after abdominal surgery. *Cochrane Database Syst Rev*. 2016; 7:Cd001893.

[137] Halabi WJ, Kang CY, Nguyen VQ, et al. Epidural analgesia in laparoscopic colorectal surgery: a nationwide analysis of use and outcomes. *JAMA Surg*. 2014; 149:130-6.

[138] Fukuda H, Tsuchida D, Koda K, Miyazaki M, Pappas TN, Takahashi T. Inhibition of sympathetic pathways restores postoperative ileus in the upper and lower gastrointestinal tract. *J Gastroenterol Hepatol*. 2007; 22:1293-9.

[139] Holte K, Kehlet H. Postoperative ileus: progress towards effective management. *Drugs*. 2002; 62:2603-15.

[140] Tanila H, Kauppila T, Taira T. Inhibition of intestinal motility and reversal of postlaparotomy ileus by selective alpha 2-adrenergic drugs in the rat. *Gastroenterology*. 1993; 104:819-24.

[141] Ferraz AA, Wanderley GJ, Santos MA, Jr., Mathias CA, Araujo JG, Jr., Ferraz EM. Effects of propranolol on human postoperative ileus. *Dig Surg*. 2001; 18:305-10.

[142] Hallerback B, Carlsen E, Carlsson K, et al. Beta-adrenoceptor blockade in the treatment of postoperative adynamic ileus. *Scand J Gastroenterol*. 1987; 22:149-55.

[143] De Winter BY, Boeckxstaens GE, De Man JG, Moreels TG, Herman AG, Pelckmans PA. Effect of adrenergic and nitrergic blockade on experimental ileus in rats. *Br J Pharmacol*. 1997; 120:464-8.

[144] Si S, Zhao X, Su F, et al. New advances in clinical application of neostigmine: no longer focusing solely on increasing skeletal muscle strength. *Front Pharmacol*. 2023; 14:1227496.

[145] Paparini D, Gori S, Grasso E, et al. Acetylcholine contributes to control the physiological inflammatory response during the peri-implantation period. *Acta Physiol (Oxf)*. 2015; 214:237-47.

[146] Gong J, Xie Z, Zhang T, et al. Randomised clinical trial: prucalopride, a colonic pro-motility agent, reduces the duration of post-operative ileus after elective gastrointestinal surgery. *Aliment Pharmacol Ther*. 2016; 43:778-89.

[147] Milne T, Liu C, O'Grady G, Woodfield J, Bissett I. Effect of prucalopride to improve time to gut function recovery following elective colorectal surgery: randomized clinical trial. *Br J Surg*. 2022; 109:704-10.

[148] Stakenborg N, Labeeuw E, Gomez-Pinilla PJ, et al. Preoperative administration of the 5-HT4 receptor agonist prucalopride reduces intestinal inflammation and shortens postoperative ileus via cholinergic enteric neurons. *Gut*. 2019; 68:1406-16.

[149] Matteoli G, Gomez-Pinilla PJ, Nemethova A, et al. A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. *Gut*. 2014; 63:938-48.

[150] Stakenborg N, Wolthuis AM, Gomez-Pinilla PJ, et al. Abdominal vagus nerve stimulation as a new therapeutic approach to prevent postoperative ileus. *Neurogastroenterol Motil*. 2017; 29.

[151] Chapman SJ, Helliwell JA, Naylor M, Tassinari C, Corrigan N, Jayne DG. Noninvasive vagus nerve stimulation to reduce ileus after major colorectal surgery: early development study. *Colorectal Dis*. 2021; 23:1225-32.

[152] Noble EJ, Harris R, Hosie KB, Thomas S, Lewis SJ. Gum chewing reduces postoperative ileus? A systematic review and meta-analysis. *Int J Surg*. 2009; 7:100-5.

[153] de Leede EM, van Leersum NJ, Kroon HM, et al. Multicentre randomized clinical trial of the effect of chewing gum after abdominal surgery. *Br J Surg*. 2018; 105:820-8.

[154] Short V, Herbert G, Perry R, et al. Chewing gum for postoperative recovery of gastrointestinal function. *Cochrane Database Syst Rev*. 2015; 2015:CD006506.

[155] Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg*. 2017; 152:292-8.

[156] Scarborough JE, Mantyh CR, Sun Z, Migaly J. Combined Mechanical and Oral Antibiotic Bowel Preparation Reduces Incisional Surgical Site Infection and Anastomotic Leak Rates After

Elective Colorectal Resection: An Analysis of Colectomy-Targeted ACS NSQIP. *Ann Surg*. 2015; 262:331-7.

[157] Modasi A, Pace D, Godwin M, Smith C, Curtis B. NSAID administration post colorectal surgery increases anastomotic leak rate: systematic review/meta-analysis. *Surg Endosc*. 2019; 33:879-85.

[158] EuroSurg Collaborative. Safety and efficacy of non-steroidal anti-inflammatory drugs to reduce ileus after colorectal surgery. *Br J Surg*. 2020; 107:e161-e9.

[159] Venara A, Duchalais E, Dariel A, et al. Anti-inflammatory Effects of Enhanced Recovery Programs on Early-Stage Colorectal Cancer Surgery. *World J Surg*. 2018; 42:953-64.

[160] Hakkarainen TW, Steele SR, Bastaworous A, et al. Nonsteroidal anti-inflammatory drugs and the risk for anastomotic failure: a report from Washington State's Surgical Care and Outcomes Assessment Program (SCOAP). *JAMA Surg*. 2015; 150:223-8.

[161] Klein M, Gogenur I, Rosenberg J. Postoperative use of non-steroidal anti-inflammatory drugs in patients with anastomotic leakage requiring reoperation after colorectal resection: cohort study based on prospective data. *BMJ*. 2012; 345:e6166.

[162] Milne TGE, Jaung R, O'Grady G, Bissett IP. Nonsteroidal anti-inflammatory drugs reduce the time to recovery of gut function after elective colorectal surgery: a systematic review and meta-analysis. *Colorectal Dis*. 2018; 20:O190-O8.

[163] Chapman SJ, Garner JJ, Drake TM, Aldaffaa M, Jayne DG. Systematic Review and Meta-analysis of Nonsteroidal Anti-inflammatory Drugs to Improve GI Recovery After Colorectal Surgery. *Dis Colon Rectum*. 2019; 62:248-56.

[164] Carli F. Physiologic considerations of Enhanced Recovery After Surgery (ERAS) programs: implications of the stress response. *Can J Anaesth*. 2015; 62:110-9.

[165] Chapman SJ, Pericleous A, Downey C, Jayne DG. Postoperative ileus following major colorectal surgery. *Br J Surg*. 2018; 105:797-810.

[166] Dudi-Venkata NN, Kroon HM, Bedrikovetski S, Moore JW, Sammour T. Systematic scoping review of enhanced recovery protocol recommendations targeting return of gastrointestinal function after colorectal surgery. *ANZ J Surg*. 2020; 90:41-7.

[167] Popescu I, Fleshner PR, Pezzullo JC, Charlton PA, Kosutic G, Senagore AJ. The Ghrelin agonist TZP-101 for management of postoperative ileus after partial colectomy: a randomized, dose-ranging, placebo-controlled clinical trial. *Dis Colon Rectum*. 2010; 53:126-34.

[168] Trudel L, Tomasetto C, Rio MC, et al. Ghrelin/motilin-related peptide is a potent prokinetic to reverse gastric postoperative ileus in rat. *Am J Physiol Gastrointest Liver Physiol*. 2002; 282:G948-52.

[169] Beck DE, Sweeney WB, McCarter MD, Ipamorelin 201 Study G. Prospective, randomized, controlled, proof-of-concept study of the Ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients. *Int J Colorectal Dis*. 2014; 29:1527-34.

[170] Wolff BG, Michelassi F, Gerkin TM, et al. Alvimopan, a novel, peripherally acting mu opioid antagonist: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial of major abdominal surgery and postoperative ileus. *Ann Surg*. 2004; 240:728-34.

[171] Viscusi ER, Goldstein S, Witkowski T, et al. Alvimopan, a peripherally acting mu-opioid receptor antagonist, compared with placebo in postoperative ileus after major abdominal surgery: results of a randomized, double-blind, controlled study. *Surg Endosc*. 2006; 20:64-70.

[172] Steele SR, Brady JT, Cao Z, et al. Evaluation of Healthcare Use and Clinical Outcomes of Alvimopan in Patients Undergoing Bowel Resection: A Propensity Score-Matched Analysis. *Dis Colon Rectum*. 2018; 61:1418-25.

[173] Herzog TJ, Coleman RL, Guerrieri JP, Jr., et al. A double-blind, randomized, placebo-controlled phase III study of the safety of alvimopan in patients who undergo simple total abdominal hysterectomy. *Am J Obstet Gynecol*. 2006; 195:445-53.

[174] Delaney CP, Weese JL, Hyman NH, et al. Phase III trial of alvimopan, a novel, peripherally acting, mu opioid antagonist, for postoperative ileus after major abdominal surgery. *Dis Colon Rectum*. 2005; 48:1114-25.

[175] Alhashemi M, Hamad R, El-Kefraoui C, et al. The association of alvimopan treatment with postoperative outcomes after abdominal surgery: A systematic review across different surgical procedures and contexts of perioperative care. *Surgery*. 2021; 169:934-44.

[176] Yu CS, Chun HK, Stambler N, et al. Safety and efficacy of methylnaltrexone in shortening the duration of postoperative ileus following segmental colectomy: results of two randomized, placebo-controlled phase 3 trials. *Dis Colon Rectum*. 2011; 54:570-8.

[177] Viscusi ER, Rathmell JP, Fichera A, et al. Randomized placebo-controlled study of intravenous methylnaltrexone in postoperative ileus. *J Drug Assess*. 2013; 2:127-34.

[178] Helander EM, Webb MP, Bias M, Whang EE, Kaye AD, Urman RD. A Comparison of Multimodal Analgesic Approaches in Institutional Enhanced Recovery After Surgery Protocols for Colorectal Surgery: Pharmacological Agents. *J Laparoendosc Adv Surg Tech A*. 2017; 27:903-8.

[179] Gomez-Izquierdo JC, Trainito A, Mirzakandov D, et al. Goal-directed Fluid Therapy Does Not Reduce Primary Postoperative Ileus after Elective Laparoscopic Colorectal Surgery: A Randomized Controlled Trial. *Anesthesiology*. 2017; 127:36-49.

[180] Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery. *N Engl J Med*. 2018; 378:2263-74.

[181] Arslan-Carlon V, Tan KS, Dalbagni G, et al. Goal-directed versus Standard Fluid Therapy to Decrease Ileus after Open Radical Cystectomy: A Prospective Randomized Controlled Trial. *Anesthesiology*. 2020; 133:293-303.

[182] Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. *Anesthesiology*. 2005; 103:25-32.

[183] Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg*. 2012; 114:640-51.

[184] Vather R, Josephson R, Jaung R, Kahokehr A, Sammour T, Bissett I. Gastrografin in Prolonged Postoperative Ileus: A Double-blinded Randomized Controlled Trial. *Ann Surg*. 2015; 262:23-30.

[185] Biondo S, Miquel J, Espin-Basany E, et al. A Double-Blinded Randomized Clinical Study on the Therapeutic Effect of Gastrografin in Prolonged Postoperative Ileus After Elective Colorectal Surgery. *World J Surg*. 2016; 40:206-14.

[186] Milne TGE, Vather R, O'Grady G, Miquel J, Biondo S, Bissett I. Gastrografin may reduce time to oral diet in prolonged post-operative ileus: a pooled analysis of two randomized trials. *ANZ J Surg*. 2018.

[187] Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. *Curr Neuropharmacol*. 2013; 11:315-35.

[188] Nair VP, Hunter JM. Anticholinesterases and anticholinergic drugs. *Continuing Education in Anaesthesia Critical Care & Pain*. 2004; 4:164-8.

[189] Baradari AG, Khajavi MR, Firouzian A, et al. Effects of combined prokinetic administration on gastric emptying in critically ill patients. *Arab J Gastroenterol*. 2017; 18:30-4.

[190] Caldarella MP, Serra J, Azpiroz F, Malagelada JR. Prokinetic effects in patients with intestinal gas retention. *Gastroenterology*. 2002; 122:1748-55.

[191] Colović MB, Krstić DZ, Lazarević-Pašti TD, Bondžić AM, Vasić VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. *Curr Neuropharmacol*. 2013; 11:315-35.

[192] Neely GA, Sabir S, Kohli A. Neostigmine. *StatPearls*. Treasure Island (FL), 2023.

[193] Maggi L, Mantegazza R. Treatment of myasthenia gravis: focus on pyridostigmine. *Clin Drug Investig*. 2011; 31:691-701.

[194] Manini ML, Camilleri M, Grothe R, Di Lorenzo C. Application of Pyridostigmine in Pediatric Gastrointestinal Motility Disorders: A Case Series. *Paediatr Drugs*. 2018; 20:173-80.

[195] Althausen PL, Gupta MC, Benson DR, Jones DA. The use of neostigmine to treat postoperative ileus in orthopedic spinal patients. *J Spinal Disord*. 2001; 14:541-5.

[196] Caliskan E, Turkoz A, Sener M, Bozdogan N, Gulcan O, Turkoz R. A prospective randomized double-blind study to determine the effect of thoracic epidural neostigmine on postoperative ileus after abdominal aortic surgery. *Anesth Analg*. 2008; 106:959-64.

[197] Valle RG, Godoy FL. Neostigmine for acute colonic pseudo-obstruction: A meta-analysis. *Ann Med Surg (Lond)*. 2014; 3:60-4.

[198] Frankel A, Gillespie C, Lu CT, Hewett P, Wattchow D. Subcutaneous neostigmine appears safe and effective for acute colonic pseudo-obstruction (Ogilvie's syndrome). *ANZ J Surg*. 2019; 89:700-5.

[199] O'Dea CJ, Brookes JH, Wattchow DA. The efficacy of treatment of patients with severe constipation or recurrent pseudo-obstruction with pyridostigmine. *Colorectal Dis*. 2010; 12:540-8.

[200] Bharucha AE, Low PA, Camilleri M, Burton D, Gehrking TL, Zinsmeister AR. Pilot study of pyridostigmine in constipated patients with autonomic neuropathy. *Clin Auton Res*. 2008; 18:194-202.

[201] Di Nardo G, Di Lorenzo C, Lauro A, et al. Chronic intestinal pseudo-obstruction in children and adults: diagnosis and therapeutic options. *Neurogastroenterol Motil*. 2017; 29.

[202] Accarino A, Perez F, Azpiroz F, Quiroga S, Malagelada JR. Intestinal gas and bloating: effect of prokinetic stimulation. *Am J Gastroenterol*. 2008; 103:2036-42.

[203] Xiao G, Xie X, Fan J, et al. Efficacy and safety of acotiamide for the treatment of functional dyspepsia: systematic review and meta-analysis. *ScientificWorldJournal*. 2014; 2014:541950.

[204] Adiamah A, Johnson S, Ho A, Orbell J. Neostigmine and glycopyrronium: a potential safe alternative for patients with pseudo-obstruction without access to conventional methods of decompression. *BMJ Case Rep*. 2017; 2017.

[205] Choudhury A, Rahyead A, Kammermeier J, Mutalib M. The Use of Pyridostigmine in a Child With Chronic Intestinal Pseudo-Obstruction. *Pediatrics*. 2018; 141:S404-S7.

[206] Luckey A, Livingston E, Tache Y. Mechanisms and treatment of postoperative ileus. *Arch Surg*. 2003; 138:206-14.

[207] Law NM, Bharucha AE, Undale AS, Zinsmeister AR. Cholinergic stimulation enhances colonic motor activity, transit, and sensation in humans. *Am J Physiol Gastrointest Liver Physiol*. 2001; 281:G1228-37.

[208] Dhar SI, Nativ-Zeltzer N, Mehdizadeh OB, Ramaswamy AT, Nachalon Y, Belafsky PC. Effects of Pyridostigmine on Esophageal and Pharyngeal Motility in Dysphagic Patients Undergoing High-Resolution Manometry. *Dysphagia*. 2022; 37:4-10.

[209] Klinge MW, Haase AM, Mark EB, et al. Colonic motility in patients with type 1 diabetes and gastrointestinal symptoms. *Neurogastroenterol Motil*. 2020; 32:e13948.

[210] Pasha SF, Lunsford TN, Lennon VA. Autoimmune gastrointestinal dysmotility treated successfully with pyridostigmine. *Gastroenterology*. 2006; 131:1592-6.

[211] Soufi-Afshar I, Moghadamnia A, Bijani A, Kazemi S, Shokri-Shirvani J. Comparison of pyridostigmine and bisacodyl in the treatment of refractory chronic constipation. *Caspian J Intern Med*. 2016; 7:19-24.

[212] Bharucha AE, Low P, Camilleri M, et al. A randomised controlled study of the effect of cholinesterase inhibition on colon function in patients with diabetes mellitus and constipation. *Gut*. 2013; 62:708-15.

[213] Murphy GS, de Boer HD, Eriksson LI, Miller R. Chapter 28: Reversal (Antagonism) of Neuromuscular Blockade. In: Gropper MA, Miller RD, (9th ed) *Miller's anesthesia*, 2020; 832-64.

[214] Cook D, Simons DJ. Neuromuscular Blockade. *StatPearls*. Treasure Island (FL): StatPearls, 2023.

[215] Hunter J, Shields M. Chapter 8: Muscle function and neuromuscular blockade. *Smith and Aitkenhead's Textbook of Anaesthesia*, 2019; 131-46.

[216] Sen A, Erdivanli B, Tomak Y, Pergel A. Reversal of neuromuscular blockade with sugammadex or neostigmine/atropine: Effect on postoperative gastrointestinal motility. *J Clin Anesth*. 2016; 32:208-13.

[217] An J, Noh H, Kim E, Lee J, Woo K, Kim H. Neuromuscular blockade reversal with sugammadex versus pyridostigmine/glycopyrrolate in laparoscopic cholecystectomy: a randomized trial of effects on postoperative gastrointestinal motility. *Korean J Anesthesiol*. 2020; 73:137-44.

[218] Deljou A, Schroeder DR, Ballinger BA, Sprung J, Weingarten TN. Effects of Sugammadex on Time of First Postoperative Bowel Movement: A Retrospective Analysis. *Mayo Clin Proc Innov Qual Outcomes*. 2019; 3:294-301.

[219] Chae YJ, Joe HB, Oh J, Lee E, Yi IK. Thirty-Day Postoperative Outcomes Following Sugammadex Use in Colorectal Surgery Patients; Retrospective Study. *J Clin Med*. 2019; 8.

[220] Hunt ME, Yates JR, Vega H, Heidel RE, Buehler JM. Effects on Postoperative Gastrointestinal Motility After Neuromuscular Blockade Reversal With Sugammadex Versus Neostigmine/Glycopyrrolate in Colorectal Surgery Patients. *Ann Pharmacother*. 2020; 54:1165-74.

[221] Schaller SJ, Fink H. Sugammadex as a reversal agent for neuromuscular block: an evidence-based review. *Core Evid*. 2013; 8:57-67.

[222] Srivastava A, Hunter JM. Reversal of neuromuscular block. *Br J Anaesth*. 2009; 103:115-29.

[223] Caldwell JE, Miller RD. Clinical implications of sugammadex. *Anaesthesia*. 2009; 64 Suppl 1:66-72.

[224] Vaghiri S, Prassas D, Krieg S, Knoefel WT, Krieg A. The Postoperative Effect of Sugammadex versus Acetylcholinesterase Inhibitors in Colorectal Surgery: An Updated Meta-Analysis. *J Clin Med*. 2023; 12.

[225] Fanaei SA, Khatami SM, Ziaee SA. Neostigmine in unavoidable post operative ileus: A randomized clinical trial. *J Clin Diagn Res*. 2008; 2.

[226] van der Spoel JI, Oudemans-van Straaten HM, Stoutenbeek CP, Bosman RJ, Zandstra DF. Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure--a prospective, double-blind, placebo-controlled trial. *Intensive Care Med*. 2001; 27:822-7.

[227] Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med*. 1999; 341:137-41.

[228] Orlando E, Finelli F, Colla M, Giotto E, Terragni P, Olivero G. Double-blind study of neostigmine en versus placebo in paralytic ileus as a reult of surgery. *Minerva Chirurgica*. 1994; 49:451-5.

[229] Arthur T, Burgess A. Acute Colonic Pseudo-Obstruction. *Clin Colon Rectal Surg*. 2022; 35:221-6.

[230] Alavi K, Poylin V, Davids JS, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colonic Volvulus and Acute Colonic Pseudo-Obstruction. *Dis Colon Rectum*. 2021; 64:1046-57.

[231] Vogel JD, Feingold DL, Stewart DB, et al. Clinical Practice Guidelines for Colon Volvulus and Acute Colonic Pseudo-Obstruction. *Dis Colon Rectum*. 2016; 59:589-600.

[232] Naveed M, Jamil LH, Fujii-Lau LL, et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the management of acute colonic pseudo-obstruction and colonic volvulus. *Gastrointest Endosc*. 2020; 91:228-35.

[233] Trevisani GT, Hyman NH, Church JM. Neostigmine: safe and effective treatment for acute colonic pseudo-obstruction. *Dis Colon Rectum*. 2000; 43:599-603.

[234] Dudi-Venkata NN, Kroon HM, Bedrikovetski S, Moore JW, Thomas ML, Sammour T. A global survey of surgeons' preferences and practice with regard to laxative use after elective colorectal surgery. *Int J Colorectal Dis*. 2020; 35:759-63.

[235] Dudi-Venkata NN, Kroon HM, Bedrikovetski S, et al. Impact of STIMUlant and osmotic LAXatives (STIMULAX trial) on gastrointestinal recovery after colorectal surgery: randomized clinical trial. *Br J Surg*. 2021; 108:797-803.

[236] Miceli PC, Jacobson K. Cholinergic pathways modulate experimental dinitrobenzene sulfonic acid colitis in rats. *Auton Neurosci*. 2003; 105:16-24.

[237] Hofer S, Eisenbach C, Lukic IK, et al. Pharmacologic cholinesterase inhibition improves survival in experimental sepsis. *Crit Care Med*. 2008; 36:404-8.

[238] Kalb A, von Haefen C, Sifringer M, et al. Acetylcholinesterase inhibitors reduce neuroinflammation and -degeneration in the cortex and hippocampus of a surgery stress rat model. *PLoS One*. 2013; 8:e62679.

[239] Sun L, Zhang GF, Zhang X, et al. Combined administration of anisodamine and neostigmine produces anti-shock effects: involvement of alpha7 nicotinic acetylcholine receptors. *Acta Pharmacol Sin*. 2012; 33:761-6.

[240] Bitzinger DI, Gruber M, Tummler S, et al. In Vivo Effects of Neostigmine and Physostigmine on Neutrophil Functions and Evaluation of Acetylcholinesterase and Butyrylcholinesterase as Inflammatory Markers during Experimental Sepsis in Rats. *Mediators Inflamm*. 2019; 2019:8274903.

[241] Akinci SB, Ulu N, Yondem OZ, et al. Effect of neostigmine on organ injury in murine endotoxemia: missing facts about the cholinergic antiinflammatory pathway. *World J Surg*. 2005; 29:1483-9.

[242] Kanashiro A, Talbot J, Peres RS, et al. Neutrophil Recruitment and Articular Hyperalgesia in Antigen-Induced Arthritis are Modulated by the Cholinergic Anti-Inflammatory Pathway. *Basic Clin Pharmacol Toxicol*. 2016; 119:453-7.

[243] Antunes GL, Silveira JS, Kaiber DB, et al. Neostigmine treatment induces neuroprotection against oxidative stress in cerebral cortex of asthmatic mice. *Metab Brain Dis*. 2020; 35:765-74.

[244] Antunes GL, Silveira JS, Kaiber DB, et al. Cholinergic anti-inflammatory pathway confers airway protection against oxidative damage and attenuates inflammation in an allergic asthma model. *J Cell Physiol*. 2020; 235:1838-49.

[245] Pinder N, Bruckner T, Lehmann M, et al. Effect of physostigmine on recovery from septic shock following intra-abdominal infection - Results from a randomized, double-blind, placebo-controlled, monocentric pilot trial (Anticholium(R) per Se). *J Crit Care*. 2019; 52:126-35.

[246] El-Tamalawy MM, Soliman MM, Omara AF, Rashad A, Ibrahim OM, El-Shishtawy MM. Efficacy and Safety of Neostigmine Adjunctive Therapy in Patients With Sepsis or Septic Shock: A Randomized Controlled Trial. *Front Pharmacol*. 2022; 13:855764.

[247] You X, Wang Y, Wu J, et al. Zusanli (ST36) Acupoint Injection with Neostigmine for Paralytic Postoperative Ileus following Radical Gastrectomy for Gastric Cancer: a Randomized Clinical Trial. *J Cancer*. 2018; 9:2266-74.

[248] Maleknejad A, Khazaei A, Bouya S. Evaluation of the Effect of Oral Pyridostigmine on the Ileus after Abdominal Surgery: A Blinded Randomized Clinical Trial. *J Clin Med*. 2018; 7.

[249] Dudi-Venkata NN, Kroon HM, Bedrikovetski S, et al. PyRICo-Pilot: pyridostigmine to reduce the duration of postoperative ileus after colorectal surgery - a phase II study. *Colorectal Dis*. 2021; 23:2154-60.

[250] Vaughan-Shaw PG, Fecher IC, Harris S, Knight JS. A meta-analysis of the effectiveness of the opioid receptor antagonist alvimopan in reducing hospital length of stay and time to GI recovery in patients enrolled in a standardized accelerated recovery program after abdominal surgery. *Dis Colon Rectum*. 2012; 55:611-20.

[251] Doorly MG, Senagore AJ. Pathogenesis and clinical and economic consequences of postoperative ileus. *Surg Clin North Am*. 2012; 92:259-72, viii.

[252] Batke M, Cappell MS. Adynamic ileus and acute colonic pseudo-obstruction. *Med Clin North Am*. 2008; 92:649-70, ix.

[253] de Jonge WJ, van der Zanden EP, The FO, et al. Stimulation of the vagus nerve attenuates macrophage activation by activating the Jak2-STAT3 signaling pathway. *Nat Immunol*. 2005; 6:844-51.

[254] Paran H, Silverberg D, Mayo A, Shwartz I, Neufeld D, Freund U. Treatment of acute colonic pseudo-obstruction with neostigmine. *J Am Coll Surg*. 2000; 190:315-8.

[255] Traut U, Brugger L, Kunz R, et al. Systemic prokinetic pharmacologic treatment for postoperative adynamic ileus following abdominal surgery in adults. *Cochrane Database Syst Rev*. 2008:CD004930.

[256] Myrhoj T, Olsen O, Wengel B. Neostigmine in postoperative intestinal paralysis. A double-blind, clinical, controlled trial. *Dis Colon Rectum*. 1988; 31:378-9.

[257] Kram B, Greenland M, Grant M, Campbell ME, Wells C, Sommer C. Efficacy and Safety of Subcutaneous Neostigmine for Ileus, Acute Colonic Pseudo-obstruction, or Refractory Constipation. *Ann Pharmacother*. 2018; 52:505-12.

[258] Garcia-Caballero M, Vara-Thorbeck C. The evolution of postoperative ileus after laparoscopic cholecystectomy. A comparative study with conventional cholecystectomy and sympathetic blockade treatment. *Surg Endosc*. 1993; 7:416-9.

[259] Hallerback B, Ander S, Glise H. Effect of combined blockade of beta-adrenoceptors and acetylcholinesterase in the treatment of postoperative ileus after cholecystectomy. *Scand J Gastroenterol*. 1987; 22:420-4.

[260] Traeger L, Koullouros M, Bedrikovetski S, Kroon HM, Moore JW, Sammour T. Global cost of postoperative ileus following abdominal surgery: meta-analysis. *BJS Open*. 2023; 7.

[261] Traeger L, Koullouros M, Bedrikovetski S, et al. Cost of postoperative ileus following colorectal surgery: A cost analysis in the Australian public hospital setting. *Colorectal Dis*. 2022; 24:1416-26.

[262] The FO, Boeckxstaens GE, Snoek SA, et al. Activation of the cholinergic anti-inflammatory pathway ameliorates postoperative ileus in mice. *Gastroenterology*. 2007; 133:1219-28.

[263] Mazzotta E, Villalobos-Hernandez EC, Fiorda-Diaz J, Harzman A, Christofi FL. Postoperative Ileus and Postoperative Gastrointestinal Tract Dysfunction: Pathogenic Mechanisms

and Novel Treatment Strategies Beyond Colorectal Enhanced Recovery After Surgery Protocols. *Front Pharmacol*. 2020; 11:583422.

[264] Beavers J, Orton L, Atchison L, et al. The Efficacy and Safety of Methylnaltrexone for the Treatment of Postoperative Ileus. *Am Surg*. 2022; 88:409-13.

[265] Madsen PV, Olsen O, Hagen K. Ceruletide and neostigmine in postoperative intestinal paralysis. A double-blind clinical controlled trial. *Dis Colon Rectum*. 1986; 29:712-3.

[266] Traeger L, Kroon HM, Bedrikovetski S, Moore JW, Sammour T. The impact of acetylcholinesterase inhibitors on ileus and gut motility following abdominal surgery: a clinical review. *ANZ J Surg*. 2022; 92:69-76.

[267] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009; 62:1006-12.

[268] Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019; 366:l4898.

[269] McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods*. 2021; 12:55-61.

[270] Australian Medicines Handbook. Pyridostigmine. Adelaide: AMH, 2023.

[271] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007; 370:1453-7.

[272] National Health and Medical Research Council (NHMRC) Australian Research Council Australian Vice-Chancellors' Committee. (2018) National statement on ethical conduct in human research. Australia: NHMRC, Canberra. Report No.: ISBN: 1864962755.

[273] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009; 250:187-96.

[274] Huisman DE, Reudink M, van Rooijen SJ, et al. LekCheck: A Prospective Study to Identify Perioperative Modifiable Risk Factors for Anastomotic Leakage in Colorectal Surgery. *Ann Surg*. 2022; 275:e189-e97.

[275] Child CS. Prevention of neostigmine-induced colonic activity. A comparison of atropine and glycopyrronium. *Anaesthesia*. 1984; 39:1083-5.

[276] Gallanosa A, Stevens J, Quick J. *Glycopyrrolate. StatPearls [Internet]*. Edition. Treasure Island (FL): StatPearls Publishing, cited 2021 Oct 11.Available from: https://www.ncbi.nlm.nih.gov/books/NBK526035/

[277] Scarth E, Smith S. *Drugs in anaesthesia and intensive care.* 5th ed. Oxford, UK: Oxford University Press, 2016.

[278] Bailey CR. Sugammadex: when should we be giving it? *Anaesthesia*. 2017; 72:1170-5.

[279] Sapci I, Hameed I, Ceylan A, et al. Predictors of ileus following colorectal resections. *Am J Surg*. 2020; 219:527-9.

[280] Rao Kadam V, Howell S. Unrestricted and Restricted Access to Sugammadex and Side Effect Profile in a Teaching Hospital Centre for Year 2014- Database Audit Study. *Anesth Pain Med*. 2018; 8:e63066.

[281] Ceretti AP, Maroni N, Longhi M, et al. Risk Factors for Prolonged Postoperative Ileus in Adult Patients Undergoing Elective Colorectal Surgery: An Observational Cohort Study. *Rev Recent Clin Trials*. 2018; 13:295-304.

[282] Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ*. 2013; 346:f1049.

[283] Reserve Bank of Australia. Inflation Calculator. RBA 2021. [Cited: 28/09/2021]Available at: https://www.rba.gov.au/calculator/annualDecimal.html

[284] Dai X, Ge X, Yang J, et al. Increased incidence of prolonged ileus after colectomy for inflammatory bowel diseases under ERAS protocol: a cohort analysis. *J Surg Res*. 2017; 212:86-93.

[285] Garfinkle R, Savage P, Boutros M, et al. Incidence and predictors of postoperative ileus after loop ileostomy closure: a systematic review and meta-analysis. *Surg Endosc*. 2019; 33:2430-43.

[286] Tyler JA, Fox JP, Dharmarajan S, et al. Acute health care resource utilization for ileostomy patients is higher than expected. *Dis Colon Rectum*. 2014; 57:1412-20.

[287] Grass F, Slieker J, Jurt J, et al. Postoperative ileus in an enhanced recovery pathway-a retrospective cohort study. *Int J Colorectal Dis*. 2017; 32:675-81.

[288] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ottawa, Canada; The Ottawa Hospital Research Institute. 2022. Cited: 4/10/2022.

[289] US Bureau of Labour Statistics. CPI Inflation Calculator. cited 4/10/2022. Available at: https://data.bls.gov/cgi-bin/cpicalc.pl

[290] Government NZ. Inflation calculator. cited 4/10/2022. Available from: https://www.rbnz.govt.nz/monetary-policy/about-monetary-policy/inflation-calculator

[291] US Dollar Exchange Rates. cited 4/10/2022. Available from: https://www.exchangerates.org.uk

[292] Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018; 27:1785-805.

[293] Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014; 14:135.

[294] *Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range*. cited 4 Oct 2022.Available from: https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html

[295] Solanki S, Chakinala RC, Haq KF, et al. Paralytic ileus in the United States: A cross-sectional study from the national inpatient sample. *SAGE Open Med*. 2020; 8:2050312120962636.

[296] Earnshaw SR, Kauf TL, McDade C, et al. Economic Impact of Alvimopan Considering Varying Definitions of Postoperative Ileus. *J Am Coll Surg*. 2015; 221:941-50.

[297] van den Heijkant TC, Costes LM, van der Lee DG, et al. Randomized clinical trial of the effect of gum chewing on postoperative ileus and inflammation in colorectal surgery. *Br J Surg*. 2015; 102:202-11.

[298] Peters EG, Smeets BJJ, Nors J, et al. Perioperative lipid-enriched enteral nutrition versus standard care in patients undergoing elective colorectal surgery (SANICS II): a multicentre, double-blind, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2018; 3:242-51.

[299] Ergina PL, Barkun JS, McCulloch P, Cook JA, Altman DG, Group I. IDEAL framework for surgical innovation 2: observational studies in the exploration and assessment stages. *BMJ*. 2013; 346:f3011.

[300] World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013; 310:2191-4.

[301] Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013; 258:1-7.

[302] Nguyen TM, Traeger L, Vather R, Overall B, Cho J, Sammour T. Double barrelled uro-colostomy versus Ileal conduit for urinary diversion following pelvic exenteration: a single centre experience. *ANZ J Surg*. 2023; 93:2450-6.

[303] Traeger L, Bedrikovetski S, Nguyen TM, et al. The impact of preoperative sarcopenia on postoperative ileus following colorectal cancer surgery. *Tech Coloproctol*. 2023; 27:1265-74.

[304] Traeger L, Hall TD, Bedrikovetski S, et al. Effect of neuromuscular reversal with neostigmine/glycopyrrolate versus sugammadex on postoperative ileus following colorectal surgery. *Tech Coloproctol*. 2023; 27:217-26.

[305] Ludbrook G, Grocott MPW, Heyman K, et al. Outcomes of Postoperative Overnight High-Acuity Care in Medium-Risk Patients Undergoing Elective and Unplanned Noncardiac Surgery. *JAMA Surg*. 2023; 158:701-8.

[306] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): the TRIPOD Statement. *Br J Surg*. 2015; 102:148-58.

[307] Jones KI, Doleman B, Scott S, Lund JN, Williams JP. Simple psoas cross-sectional area measurement is a quick and easy method to assess sarcopenia and predicts major surgical complications. *Colorectal Dis*. 2015; 17:O20-6.

[308] Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol*. 2011; 12:489-95.

[309] Gravesteijn BY, Nieboer D, Ercole A, et al. Machine learning algorithms performed no better than regression models for prognostication in traumatic brain injury. *J Clin Epidemiol*. 2020; 122:95-107.

[310] Christodoulou E, Ma J, Collins GS, Steyerberg EW, Verbakel JY, Van Calster B. A systematic review shows no performance benefit of machine learning over logistic regression for clinical prediction models. *J Clin Epidemiol*. 2019; 110:12-22.

[311] Khemphila A, Boonjing V. Comparing performances of logistic regression, decision trees, and neural networks for classifying heart disease patients. *2010 International Conference on Computer Information Systems and Industrial Management Applications (CISIM)*, 2010; 193-8.

[312] Monsalve-Torra A, Ruiz-Fernandez D, Marin-Alonso O, Soriano-Paya A, Camacho-Mackenzie J, Carreno-Jaimes M. Using machine learning methods for predicting inhospital mortality in patients undergoing open repair of abdominal aortic aneurysm. *J Biomed Inform*. 2016; 62:195-201.

[313] Aries P, Huet O. Ileus in the critically ill: causes, treatment and prevention. *Minerva Anestesiol*. 2020; 86:974-83.

[314] Vather R, Bissett IP. Risk factors for the development of prolonged post-operative ileus following elective colorectal surgery. *Int J Colorectal Dis*. 2013; 28:1385-91.

[315] Vergara-Fernandez O, Trejo-Avila M, Salgado-Nesme N. Sarcopenia in patients with colorectal cancer: A comprehensive review. *World J Clin Cases*. 2020; 8:1188-202.

[316] Pin F, Couch ME, Bonetto A. Preservation of muscle mass as a strategy to reduce the toxic effects of cancer chemotherapy on body composition. *Curr Opin Support Palliat Care*. 2018; 12:420-6.

[317] Trejo-Avila M, Bozada-Gutierrez K, Valenzuela-Salazar C, Herrera-Esquivel J, Moreno-Portillo M. Sarcopenia predicts worse postoperative outcomes and decreased survival rates in patients with colorectal cancer: a systematic review and meta-analysis. *Int J Colorectal Dis*. 2021; 36:1077-96.

[318] Sasaki M, Fukuoka T, Shibutani M, Sugimoto A, Maeda K, Ohira M. Usefulness of the skeletal muscle index in postoperative ileus of colorectal cancer patients: a retrospective cohort study. *BMC Surg*. 2022; 22:448.

[319] Reisinger KW, van Vugt JL, Tegels JJ, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Ann Surg*. 2015; 261:345-52.

[320] Zhang X, Wang S, Ji W, et al. The effect of prehabilitation on the postoperative outcomes of patients undergoing colorectal surgery: A systematic review and meta-analysis. *Front Oncol*. 2022; 12:958261.

[321] Traeger L, Bedrikovetski S, Nguyen TM, Moore JW, Sammour T. Incidence and associated morbidity of sarcopenia in non-malignant small and large bowel anastomosis: propensity score-matched analysis. *Int J Colorectal Dis*. 2023; 38:159.

[322] Baker DM, Chapman SJ, Thomas BD, et al. Formation of a conceptual framework during the development of a patient-reported outcome measure for early gastrointestinal recovery: phase I of the PRO-diGi study. *Colorectal Dis*. 2023; 25:2024-32.