blood advances

TO THE EDITOR:

RBC transfusion dependency refines the Molecular International Prognostic Scoring System for myelodysplastic syndrome

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Red blood cell (RBC) transfusion remains an important cornerstone of myelodysplastic syndrome (MDS) management. Approximately 30% to 40% of patients with MDS are RBC transfusion dependent (RBC-TD), which serves as a surrogate marker for ineffective erythropoiesis and inflammation and is associated with poor survival.[1,2] Despite this, neither the International Prognostic Scoring System (IPSS) nor the revised IPSS incorporate RBC-TD. We have previously shown that the dynamic assessment of RBC-TD predicts poor prognosis independent of the revised IPSS and should be considered in treatment decision-making.[2] Similarly, the European LeukemiaNet Guidelines for MDS also recommend that RBC-TD be considered when planning treatment, including consideration for allogeneic stem cell transplantation.[3]

The Molecular IPSS (IPSS-M) for MDS integrates the mutation profiling in addition to blood counts, blast percentage and cytogenetics and stratifies patients into very low, low, moderate low, moderate high, high, and very high categories with distinct survival outcomes.[4] With increasing access to next-generation sequencing, the IPSS-M is expected to be widely implemented for treatment decisions. However, the IPSS-M also does not include RBC-TD as a risk factor in its model.

To address these gaps, we evaluated the prognostic impacts of the IPSS-M and RBC-TD in 461 patients, including those with MDS (n = 398 [86.3%]) and MDS/myeloproliferative neoplasm overlap (n = 63 [13.7%]) enrolled in the South Australian Myeloid Neoplasm registry with available somatic mutation profiling. For genes with missing information, the mean variable weight calculated in the foundational data set of the IPSS-M was assigned.[4]

RBC-TD was defined as ≥8 RBC units within a 16-week period, which aligns with the "high transfusion burden" definition proffered by the International Working Group for hematologic response criteria.[5] The clinical criteria for RBC transfusion in patients with anemia remained consistent during the study period (supplemental Methods). Institutional ethics committee approvals were obtained, and procedures were followed in accordance with the revised Declaration of Helsinki.

The median age of the patients at diagnosis was 71 years (interquartile range, 64-78), and 300 patients (65.1%) were male (supplemental Table 1). Most patients (63.1% [n = 461]) were managed with supportive care, 24.5% (n = 113) had hypomethylating agents (HMAs), and 8.9% (n = 41) underwent allogeneic stem cell transplantation. The median follow-up was 89.6 months (95% confidence interval [CI], 72.6-118), and the median overall survival (OS) was 39.6 months (95% CI, 32.6-46.0).

TP53 mutations (*TP53*^{mut}) were observed in 72 patients (15.6%). Of those, 53 patients (73.6%) had multihit *TP53*^{mut}, whereas 19 (26.4%) had single-hit *TP53*^{mut} (supplemental Figure 1), as previously reported.[6] The frequency of multihit *TP53*^{mut} was 0%, 0%, 0%, 2.5%, 9.1%, and 56.3% among

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Additional methods and data can be found in the supplemental. Original data are available on request from the corresponding author, Devendra Hiwase (devendra.hiwase@sa.gov.au).

The full-text version of this article contains a data supplement.

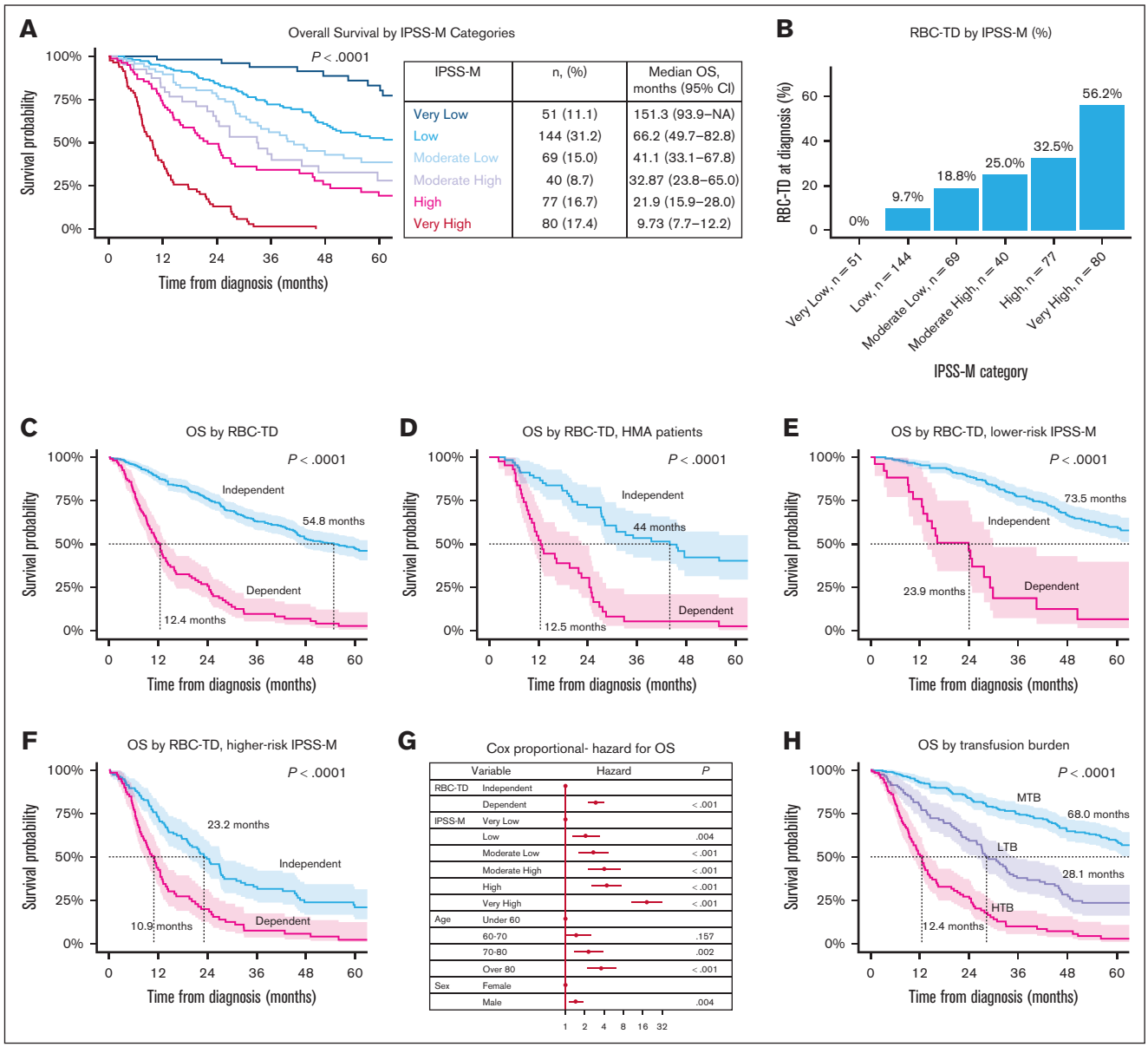

Figure 1. RBC-TD is associated with poor prognosis independent of the IPSS-M. (A) OS was progressively shorter in higher-risk IPSS-M categories. (B) The rate of RBC-TD increases with higher-risk IPSS-M. RBC-TD was associated with poor OS in the whole cohort (C), HMA-treated patients (D), and lower- (E), and higher-risk (F) IPSS-M subgroups. (G) In a multivariable Cox proportional hazards analysis, RBC-TD was associated with poor OS independent to IPSS-M category, age at diagnosis, and sex. (H) Importantly, patients with LTB and HTB groups had poorer prognosis compared with patients with MTB. MTB, minimal transfusion burden; NA, not available.

patients classified into very low, low, moderate low, high, moderate high, and very high IPSS-M risk groups, respectively.

The distribution and survival of IPSS-M categories were similar to those reported in the pivotal study by Bernard et al.[4] We also observed progressively shorter median OS with higher-risk IPSS-M categories (Figure 1A). During the study period, 84.2% of patients (n = 388) required at least 1 RBC unit, and 23.2% (n = 107) were RBC-TD at diagnosis. The frequency of patients who were RBC-TD at diagnosis increased progressively in higher-risk IPSS-M categories (Figure 1B), and HMA-treated patients were more likely to be RBC-TD (39.0% vs 18.1%; $P < .0001$). Importantly, RBC-TD was associated with poor OS in the whole cohort (12.4 vs 54.8 months; $P < .0001$) and in HMA-treated patients (12.5 vs 44.0 months; $P < .0001$; Figure 1C-D).

Having observed the poor prognosis of RBC-TD, we investigated whether RBC-TD predicts poor outcomes in the lower-risk IPSS-M categories. Because of the relatively small number of RBC-TD patients in the very low, low, and moderate low-risk IPSS-M groups (Figure 1B), we combined these patients into a lower-risk IPSS-M category. The moderate high, high, and very high-risk groups were combined into a higher-risk category. RBC-TD was observed in 27 of 264 (10.2%) lower-risk and 80 of 197 (40.6%) higher-risk (n = 197) IPSS-M patients ($P < .0001$). Importantly, RBC-TD was associated with poor prognosis in both lower- and

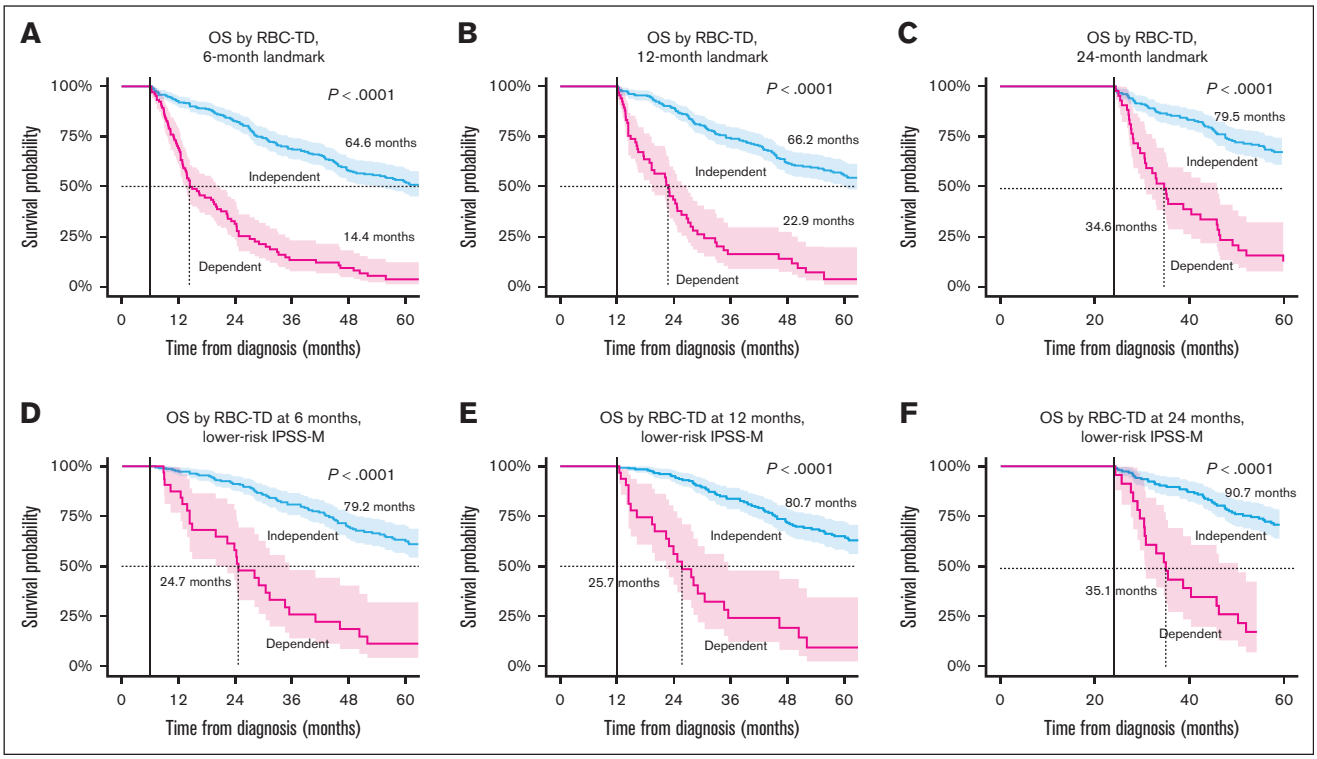

Figure 2. Dynamic assessment of RBC-TD predicts poor survival. RBC-TD status at 6, 12, and 24 months from diagnosis is associated with poor survival in the whole cohort (A-C) and IPSS-M lower-risk patients (D-F).

higher-risk IPSS-M subgroups (Figure 1E-F). Notably, the prognostic impact of RBC-TD was more pronounced in the lower-risk group compared with the higher-risk group. The median OS for lower-risk IPSS-M patients was significantly poorer in those with RBC-TD compared with RBC transfusion-independent patients (23.9 vs 73.5 months; $P < .0001$), with a prognosis comparable to higher-risk IPSS-M RBC transfusion-independent patients (23.9 vs 23.2 months; $P = .22$; Figure 1E-F). The poor prognosis of RBC-TD (hazard ratio, 2.98; 95% CI, 2.23-3.98) was further confirmed in a multivariable Cox proportional hazards, independent of the IPSS-M risk category, diagnosis, age, and sex (Figure 1G).

Next, we assessed whether the severity of RBC transfusion affects survival outcomes. For this analysis, RBC-TD was categorized into minimal transfusion burden, low transfusion burden (LTB), and high transfusion burden (HTB), based on the number of units required over 16 weeks (0-2, 3-7, and ≥8 units, respectively). Importantly, both LTB and HTB groups had poorer prognosis compared with minimal transfusion burden patients across the entire cohort, as well as in the IPSS-M lower-risk and higher-risk cohort (Figure 1H; supplemental Figure 2A-B). Notably, OS was poorer in HTB compared with LTB patients in both the whole cohort and the IPSS-M lower-risk group. However, in the higher-risk group, OS was equally poor in both LTB and HTB cases (supplemental Figure 2A-B).

RBC transfusion requirements are dynamic across the MDS disease trajectory; hence, we assessed RBC-TD at 6-, 12-, and 24-month landmark time points. We observed that 105 of 420 patients (25%) alive at 6 months, 68 of 358 (19%) alive at 12 months, and 43 of 246 (17.5%) alive at 24 months were RBC-TD. Importantly, at each landmark time point, RBC-TD was associated with poor prognosis in the whole cohort (Figure 2A-C), and lower-risk IPSS-M patients (Figure 2D-F; supplemental Table 2). Importantly, multivariable Cox proportional hazards analysis at these landmark time points validated the poor prognosis of patients who were RBC-TD, independent of the IPSS-M, diagnosis, age, and sex (supplemental Tables 3-6).

Our study demonstrates the prognostic utility of RBC-TD in MDS, independent of the IPSS-M. Similarly, in a Swedish MDS cohort, RBC transfusion within 8 months of diagnosis predicted poor survival and leukemic transformation independent of the IPSS-M.[7] However, this Swedish study defined RBC-TD as 1 unit within 4 months, which is less stringent than other accepted definitions.[2,7,8] Although there are a multitude of definitions of RBC-TD in the MDS literature, our study follows the International Working Group definition of HTB.[5] It is notable that, at the 12-month landmark, the difference in median OS between RBC-TD and transfusion-independent patients appears larger using the stringent definition used by this study compared with the definitions of 1 unit within 4 months or 1 unit every 8 weeks for 4 months.[2,7,8] Our study provides compelling evidence for progressively worsening survival with increasing RBC transfusion burden in the whole cohort and validates the poor prognosis of RBC-TD in HMA-treated patients with MDS. In addition, the prognostic impact of RBC-TD is significantly greater in the lower-risk IPSS-M group.

A limitation of this analysis is the absence of partial tandem duplication of the mixed lineage leukemia gene from our somatic panel. Overall, this study provides compelling evidence that dynamic assessment and reassessment of RBC-TD throughout a patient's

disease course predicts poor OS in MDS and MDS/myeloproliferative neoplasm independent of the IPSS-M. RBC-TD should be considered in treatment decisions, particularly by noting the poor outcomes of TD lower-risk IPSS-M patients.

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References

1. McQuilten ZK, Polizzotto MN, Wood EM, Sundararajan V. Myelodysplastic syndrome incidence, transfusion dependence, health care use, and complications: an Australian population-based study 1998 to 2008. *Transfusion*. 2013;53(8):1714-1721.
2. Hiwase DK, Singhal D, Strupp C, et al. Dynamic assessment of RBC-transfusion dependency improves the prognostic value of the revised-IPSS in MDS patients. *Am J Hematol*. 2017;92(6):508-514.
3. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood*. 2017;129(13):1753-1762.
4. Bernard E, Tuechler H, Greenberg PL, et al. Molecular International Prognostic Scoring System for myelodysplastic syndromes. *NEJM Evid*. 2022;1(7):EVIDoa2200008.
5. Platzbecker U, Fenaux P, Adès L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood*. 2019;133(10):1020-1030.
6. Shah MV, Hung KMFF, Baranwal A, et al. Evidence-based risk stratification of myeloid neoplasms harboring TP53 mutations. *Blood Adv*. Published online 14 March 2025. https://doi.org/10.1182/bloodadvances.2024015238
7. Creignou M, Bernard E, Gasparini A, et al. Early transfusion patterns improve the Molecular International Prognostic Scoring System (IPSS-M) prediction in myelodysplastic syndromes. *J Intern Med*. 2024;296(1):53-67.
8. Malcovati L, Della Porta MG, Strupp C, et al. Impact of the degree of anemia on the outcome of patients with myelodysplastic syndrome and its integration into the WHO classification-based Prognostic Scoring System (WPSS). *Haematologica*. 2011;96(10):1433-1440.