Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Prognostic Implications of Red Blood Cell Distribution Width to Albumin Ratio in Myelofibrosis: A 10-Year Multicenter and Retrospective Study

Tian Zeng[1,*], Zhikang Zheng[1,2,*], Honglan Qian[3,*], Lirong Liu[4,*], Xiaowei Shi[5,*], Yanping Shao[6,*], Zhaohao Huang[7], Rumeng Li[1], Bingbing Wen[1], Qingmei Han[1,8], Qiutian Feng[1,2], Lingrong Tu[1,2], Xiaojing Bao[1,2], Hongyan Tong[1], Jie Jin[1], Jian Huang[1]

[1]Department of Hematology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China; [2]Department of Hematology, The Fourth Affiliated Hospital, Zhejiang University School of Medicine, Yiwu, Zhejiang, People's Republic of China; [3]Department of Hematology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [4]Department of Hematology, The Affiliated Hangzhou First People's Hospital, Westlake University School of Medicine, Hangzhou, Zhejiang, People's Republic of China; [5]Department of Hematology, The Affiliated People's Hospital of Ningbo University, Ningbo, Zhejiang, People's Republic of China; [6]Department of Hematology, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Taizhou, Zhejiang, People's Republic of China; [7]Department of Hematology, Xiangshan First People's Hospital, Ningbo, Zhejiang, People's Republic of China; [8]Department of Pathology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jian Huang; Hongyan Tong, Department of Hematology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, 310003, Zhejiang, People's Republic of China, Email househuang@zju.edu.cn; tonghongyan@zju.edu.cn

Introduction: Myelofibrosis (MF) is a rare myeloproliferative neoplasm (MPN) characterized by significant mortality and limited predictive biomarkers. The red cell distribution width to albumin ratio (RAR), a novel biomarker indicative of inflammation, has emerged as a strong prognostic indicator in the general population but remains unexplored in MF.

Methods: We retrospectively enrolled 504 consecutive MF patients from 7 hematological centers over a 10-year period. Multivariate Cox regressions were performed to assess the prognostic value of the RAR. Kaplan-Meier and restricted cubic splines (RCS) analyses were further performed to examine the associations between RAR and outcomes. Interaction and subgroup analyses were conducted to explore potential effect modifiers. We developed a predictive nomogram combining RAR and DIPSS-plus, with its incremental improvements assessed by discrimination and calibration metrics.

Results: Patients who experienced leukemic transformation and death had significantly higher RAR levels. RAR remained an independent predictor of poor survival (adjusted HR: 1.58, 95% CI: 1.36–1.85). RCS further suggested a positive non-linear association between RAR and overall survival. Adding RAR to DIPSS-plus score significantly improved prediction accuracy, as shown by an increased C-index from 0.709 to 0.762, a net reclassification improvement (31.1%, $p = 0.004$), and an integrated discrimination improvement (6.80%, $p < 0.001$). The refined model also demonstrated a significantly improved goodness of fit, as evidenced by a likelihood ratio test ($p < 0.001$) and reductions in AIC and BIC values.

Conclusion: This large, multi-center cohort study is the first to reveal the prognostic significance of RAR in MF. The modified predictive nomogram combining DIPSS-plus score and RAR enhances prognostic discrimination and calibration, providing a simple yet cost-effective tool for refined risk stratification, especially in resource-limited settings.

Keywords: myelofibrosis, inflammation, nutrition, prognosis, the red cell distribution width to albumin ratio

Received: 11 March 2025
Accepted: 3 July 2025
Published: 15 July 2025

Introduction

Myelofibrosis (MF) can be classified as either primary (PMF) or secondary (SMF), with the latter evolving from polycythemia vera (PV) or essential thrombocythemia (ET).[1] As the most aggressive subtype of *BCR/ABL*-negative myeloproliferative neoplasms (MPNs), MF is associated with reduced survival and is accompanied by burdensome symptoms that significantly compromise quality of life.[2] The disease course of MF is highly variable, but it generally advances to a state characterized by profound cytopenia and eventually evolves to an acute phase, resembling acute myeloid leukemia.[3] Specifically, MF patients who experience leukemic transformation carry a dismal prognosis, with a median survival of less than 3 months and mortality rates reaching approximately 98%.[4]

JAK inhibitors (JAKis), particularly ruxolitinib, have improved outcomes for MF patients by alleviating symptoms and providing survival advantages.[5] However, there is limited evidence to suggest that JAKis can cure the disease without hematopoietic transplantation or prevent its progression to leukemia.[6] The aggressive nature and significant mortality of MF, despite treatment, underscores the urgent need for reliable prognostic tools to predict mortality and optimize clinical management. Particularly, the development of Dynamic International Prognostic Scoring System (DIPSS) and its updated version, DIPSS-plus, which incorporates unfavorable karyotypes, is a recognized milestone in MF prognosis.[7–9] However, despite their high accessibility, these methods focus on traditional hematologic parameters—white blood cells (WBC), hemoglobin (HGB), platelets (PLT), and peripheral blood blasts (PBB)—which mainly reflect hematopoietic function and disease burden but overlook broader conditions like nutritional status and systemic inflammation. In short, MF is associated with significant mortality, yet economic, accessible and multidimensional predictive biomarkers remain scarce. Therefore, identifying other cost-effective biomarkers that reflect different aspects of disease status may help refine risk stratification and guide therapeutic decisions.

Anisocytosis, especially represented by dacryocytes, is a typical feature of MF.[10] Red cell distribution width (RDW), a quantitative marker of anisocytosis routinely provided in complete blood counts, reflects variability in erythrocyte size.[11] Elevated RDW at diagnosis has been demonstrated to have prognostic significance in MF, correlating with poorer overall survival (OS).[12,13] Moreover, baseline serum albumin, a general indicator associated with the degree of cachexia and malnutrition,[14] has been identified as a prognostic factor in MF.[15] Red cell distribution width to albumin ratio (RAR), a combination of the two readily available clinical parameters, has been demonstrated to be associated with an increased risk of all-cause mortality in the general population as a novel inflammatory biomarker.[16]

In parallel, several other inflammation-related or compound indices, such as neutrophil-to-lymphocyte ratio,[17,18] Triple A score (AAA: Age, absolute neutrophil count and absolute lymphocyte count),[19] platelet-to-lymphocyte ratio,[20] as well as absolute basophil counts,[21] have been explored as prognostic indicators in MF. However, the prognostic implication of RAR has not been reported in MF patients. Therefore, we aimed to explore the predictive value of RAR for OS in MF patients. Additionally, we assessed whether integrating RAR into traditional prognostic scores (DIPSS and DIPSS-plus) improves prognostic accuracy. Eventually, we aimed to develop a prognostic nomogram based on RAR, providing a simple yet cost-effective tool for refined risk stratification.

Materials and Methods

Study Population

We retrospectively enrolled consecutive MF patients who were regularly followed up during 2013.10.01–2023.09.01 at 7 hematological centers in Zhejiang Province, China. According to the World Health Organization (WHO) 2016 criteria, PMF and SMF were diagnosed through re-evaluations by local experienced hematopathologists for the pathology of the bone marrow biopsy in combination with the indicators at the time of diagnosis.[22] Patients who had undergone bone marrow aspirations and biopsies with regular follow-ups were included in the study. There were 610 eligible patients included in this cohort. The exclusion criteria were as follows: 1) patients without RDW and/or albumin data, 2) patients without G-banding karyotype results, and 3) patients without test results on *JAK2* V617F mutations. Eventually, 504 patients were included in the final analysis.

This study was approved by the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University Institutional Review Board, and was conducted in compliance with the Declaration of Helsinki. Written informed consent was waived by the local institutional ethics committee due to the retrospective nature of the study and the use of anonymized data (2022, No492).

Data Collection and Definitions

Demographic and clinical data, including the presence of transfusion dependence, constitutional symptoms and cardiovascular risk factors (CVRs), and a history of smoking and drinking, were retrospectively retrieved from the electronic medical records. Bone marrow aspiration and biopsy were performed at diagnosis. WBC, HGB, PLT, PBB, RDW and albumin levels were measured at disease presentation. Cytogenetic analysis of bone marrow or peripheral blood samples was performed using G-banding techniques. Driver genes, including *JAK2* V617F, *MPL*, and *CALR*, were detected using Sanger sequencing of DNA extracted from bone marrow or peripheral blood samples.

Constitutional symptoms are defined as weight loss >10% of the baseline value in the year preceding MF diagnosis and/or unexplained fever or excessive sweating persisting for more than 1 month.[23] Unfavorable karyotypes were defined as complex karyotypes or one or two abnormalities, including +8, −7/7q-, i(17q), −5/5q-, 12p-, inv (3) or 11q23 rearrangements.[8] Splenomegaly was defined as an ultrasonic thickness exceeding 4 cm and/or a length exceeding 12 cm.[24]

The major outcome was OS, and the secondary outcome was leukemic transformation, which was defined according to the 2016 WHO criteria.[22] Patients were followed from diagnosis until death, or the date of the last valid follow-up. Each patient was assigned a prognostic score and stratified according to DIPSS score and DIPSS-plus score.

Statistical Analysis

Statistical analyses were performed with the SPSS software (version 25.0) and R software (version 4.2.2). Continuous variables were presented as medians (interquartile ranges [IQRs]) and compared via the Mann–Whitney *U*-tests or the Kruskal–Wallis tests. Categorical variables are presented as numbers (percentages) and were analyzed by $\chi 2$ test or Fisher's exact test.

The subjects were grouped into tertiles according to their RAR values. The group-specific distributions of RAR were visualized using raincloud plots and stacked bar plots. Cox proportional hazards regressions were performed to test the predictive ability of the variables. *p* trends were computed for the categorical RAR as tertiles in the regressions. To better interpret the regression results and minimize the impact of unit differences, RAR was standardized to assess the HR change for per SD increase in RAR. In multivariate analyses, Model 1 was adjusted for age and sex, Model 2 was adjusted for the DIPSS risk category, and Model 3 was adjusted for the DIPSS-plus risk category. Leukemia-free survival (LFS) and OS were estimated using the Kaplan–Meier method, and differences between RAR tertiles were compared with Log rank tests. Subsequently, restricted cubic splines (RCS) with 4 knots (at 5th, 35th, 65th, and 95th percentiles) were plotted to examine the potential nonlinear associations between RAR and outcomes using the rms R package. The median RAR was set as the reference (HR = 1.00). The receiver operator characteristic (ROC) analyses were performed to evaluate the prognostic value of RAR in predicting survival, and the optimal RAR threshold was determined by the maximum Youden index.

Additionally, interaction and subgroup analyses were performed to assess modifying factors of the observed associations and to determine the applicability of RAR across different subgroups. We carried out subgroup analyses on the basis of patient age (<65 vs ≥65 years), sex (female vs male), MF subtype (PMF vs SMF), transfusion dependence (yes vs no), constitutional symptoms (yes vs no), smoking status (yes vs no), drinking status (yes vs no), *JAK2* V617F mutation status (yes vs no), unfavorable karyotype status (yes vs no), WBC (>25 vs ≤25), HGB (≥100 vs <100), PLT (≥100 vs <100), and PBB (≥1% vs <1%). Variables with *p* interaction <0.05 were considered potential effect modifiers.

A nomogram was constructed via the survival package in R. Incremental improvements in survival prediction by integrating RAR into DIPSS and DIPSS-plus were evaluated through measures of discrimination and calibration. Discrimination was assessed using the C-index, continuous net reclassification improvement (cNRI), and integrated discrimination improvement (IDI). Calibration was assessed via likelihood-ratio (L-R) tests, the Akaike information criterion (AIC), the Bayesian information criterion (BIC), and calibration plots. The computations of the C-index, AIC, and BIC, along with L-R tests, were performed via the survival package. Comparisons of the cNRI and IDI were implemented using the survIDINRI package. Visualization of the C-index and its confidence intervals, as well as the generation of calibration curves, was conducted with the ggplot2 package. A *p* value <0.05 was considered as statistical significance.

Results

Patient Overview

After selection, a total of 504 MF patients from 7 hematological centers were eventually enrolled in this study (Figure 1). The median age at diagnosis was 64 years (IQR: 54–70), with 281 (55.8%) patients being male. Among the total cohort, 360 (71.4%) patients were classified as PMF, and 356 (70.6%) patients had *JAK2* V617F mutations. During the follow-up period, 79 (15.7%) patients developed leukemic transformation, and 142 (28.2%) died. The baseline and clinical characteristics of patients stratified by tertiles of RAR are summarized in Table 1. Transfusion-dependent patients were more frequent in higher RAR tertiles (Tertile 1:11.9%, Tertile 2: 28.0%, Tertile 3: 41.70%; $p < 0.001$). The proportion of patients with CVRs and unfavorable karyotypes varied significantly across RAR tertiles ($p = 0.045$, $p = 0.014$). The median HGB (Tertile 1: 122; Tertile 2: 99; Tertile 3: 83; $p < 0.001$) and PLT (Tertile 1: 321; Tertile 2: 226; Tertile 3: 222; $p = 0.004$) decreased across RAR tertiles, suggesting more severe anemia and impaired thrombopoiesis with higher RAR levels. The risk of adverse outcomes increased with higher RAR tertiles. The incidence of leukemic transformation increased from 9.5% in the 1st tertile to 11.9% and 25.6% in the 2nd and 3rd tertiles, respectively ($p < 0.001$). Similarly, a stepwise decline in survival was observed across RAR tertiles, with mortality rates of 13.7%, 22.0%, and 48.8% for the 1st, 2nd, and 3rd tertile, respectively ($p < 0.001$).

Distributions of RAR

Patients who developed leukemic transformation had significantly higher RAR compared to those without transformation (median: 5.20 vs 4.44, $p < 0.001$) (Figure 2A). Similarly, RAR in non-survivors was significantly higher in survivors (median: 5.31 vs 4.27, $p < 0.001$) (Figure 2B).

Among patients stratified by DIPSS, we noticed a transition from a greater proportion of low- and intermediate-1-risk patients in Tertile 1 (140/168, 83.33%) to predominantly intermediate-2- or higher-risk patients in Tertile 3 (105/168, 62.50%) (Figure 2C). Additionally, the integration of unfavorable karyotypes, transfusion dependence, and PLT counts in DIPSS-plus

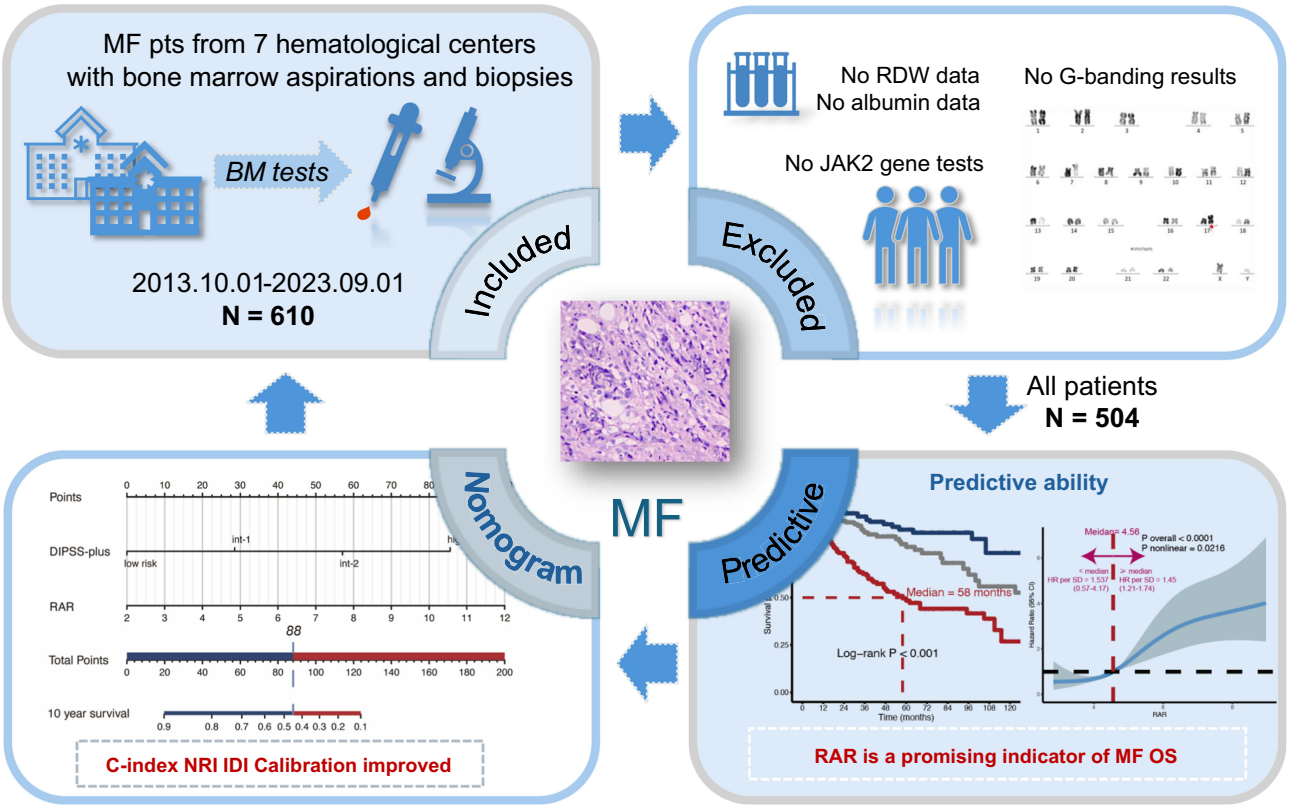

Figure 1 Study Flow Diagram.

Table 1 Characteristics of the Study Population Stratified by RAR Tertiles

	Total	Tertile 1 [2.39–4.11)	Tertile 2 [4.11–5.16)	Tertile 3 [5.16–11.5]	*p* value
N	504	168	168	168	
Age at diagnosis (years)	64 (54–70)	58 (50–67)	66 (58–71)	65 (56–73)	< 0.001
Male (%)	281 (55.8%)	89 (53.0%)	95 (56.5%)	97 (57.7%)	0.658
PMF (%)	360 (71.4%)	120 (71.4%)	126 (75.0%)	114 (67.9%)	0.350
Clinical characteristics					
Transfusion dependence (%)	137 (27.2%)	20 (11.9%)	47 (28.0%)	70 (41.7%)	< 0.001
Constitutional symptoms (%)	170 (33.7%)	55 (32.7%)	61 (36.3%)	54 (32.1%)	0.683
Smoking (%)	101 (20.0%)	27 (16.1%)	39 (23.2%)	35 (20.8%)	0.250
Drinking (%)	98 (19.4%)	30 (17.9%)	40 (23.8%)	28 (16.7%)	0.208
CVRs (%)	228 (45.2%)	63 (37.5%)	84 (50.0%)	81 (48.2%)	0.045
Splenomegaly (%)	425 (84.3%)	134 (79.8%)	149 (88.7%)	142 (84.5%)	0.079
Laboratory characteristics					
JAK2 mutation (%)	356 (70.6%)	117 (69.6%)	122 (72.6%)	117 (69.6%)	0.787
Unfavorable karyotypes (%)	70 (13.9%)	13 (7.7%)	26 (15.5%)	31 (18.5%)	0.014
WBC	10 (5–20)	10 (6–18)	10 (5–19)	10 (5–20)	0.945
HGB	102 (80–127)	122 (104–139)	99 (80–117)	83 (67–104)	< 0.001
PLT	259 (112–515)	321 (168–584)	226 (99–535)	222 (92–458)	0.004
PBB	0.00 (0.00–1.00)	0.00 (0.00–0.13)	0.00 (0.00–1.00)	0.00 (0.00–2.00)	0.007
RDW	18.6 (16.5–21.1)	16.1 (14.6–17.6)	18.9 (17.3–20.3)	21.8 (19.8–24.8)	< 0.001
Albumin	42 (37–45)	45 (43–48)	41 (38–44)	36 (31–40)	< 0.001
Outcomes					
Leukemic transformation (%)	79 (15.7%)	16 (9.5%)	20 (11.9%)	43 (25.6%)	< 0.001
Death (%)	142 (28.2%)	23 (13.7%)	37 (22.0%)	82 (48.8%)	< 0.001

Abbreviations: RAR, red cell distribution width-to-albumin ratio; PMF, primary myelofibrosis; CVRs, cardiovascular risk factors; WBC, white blood cells; HGB, hemoglobin; PLT, platelet; PBB, peripheral blood blasts; RDW, red cell distribution width.

score resulted in a shift in risk stratification. Compared with DIPSS, for DIPSS-plus score, a larger proportion of patients in each tertile were classified as intermediate-2 or higher risk (Tertile 1: 30.36% vs 16.67%, Tertile 2: 61.31% vs 49.40%, Tertile 3: 77.98% vs 62.50%), reflecting the refined prognostic accuracy of the updated system (Figure 2D). In short, the RAR was associated with a worsening of risk categories either stratified by DIPSS score or DIPSS-plus score.

Associations Between RAR and Outcomes

Considering that the DIPSS and DIPSS-plus scores were originally designed for PMF rather than SMF patients, the subsequent Cox proportional hazards regression analyses adjusted for DIPSS and DIPSS-plus scores were performed upon 360 PMF patients (Table 2). Tertile 3 of RAR was associated with a 5.06-fold increased risk of mortality compared to tertile 1 (HR = 5.06, 95% CI = 3.03–8.46, $p < 0.001$) in the unadjusted model. With per SD increase in RAR, the risk for mortality increased by 73% (HR = 1.73, 95% CI = 1.51–1.99, $p < 0.001$).

In multivariate analyses, model 1 was adjusted for age and sex, model 2 was adjusted for DIPSS risk category, model 3 was adjusted for DIPSS-plus risk category. Notably, a significant trend of RAR tertile was revealed in all models (p trend < 0.001). After adjusting for age and sex, the risk for mortality increased 3.40-fold in tertile 3 patients (HR = 4.40, 95% CI: 2.62–7.39). After adjusting for DIPSS risk category and DIPSS-plus risk category, the HRs were 1.66 (95% CI = 1.43–1.92) and 1.58 (95% CI = 1.36–1.85) for per SD increase in the RAR, respectively (Table 2).

The LFS and OS curves stratified by RAR tertiles are presented in Figure 3A and B, respectively. In our cohort, the median LFS was 179.00 months (95% CI: 144.38–213.62), and the median OS was 123.00 months (95% CI: 95.35–150.65), indicating a relatively low baseline risk of adverse outcomes. However, significant differences in LFS and OS were observed across RAR tertiles (log-rank $p < 0.001$). The tertile 1 and 2 group did not reach median LFS, whereas tertile 3 had a median LFS of 114 months (Figure 3A). Notably, the median OS reduced to 58.00 months in tertile 3, suggesting that patients in tertile 3 represent a high-risk group with significantly worse outcomes (Figure 3B).

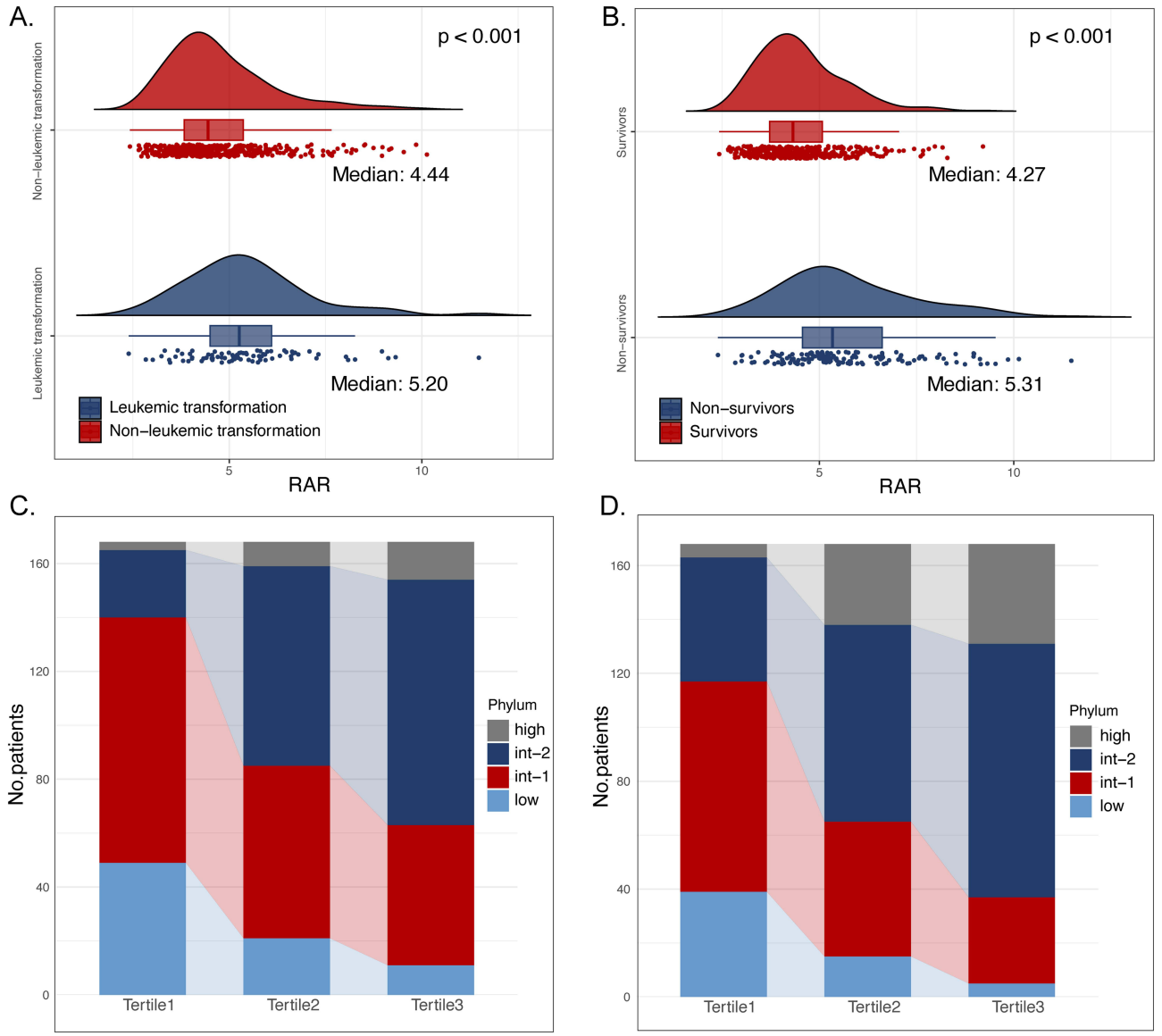

Figure 2 Distributions of RAR.
Notes: (**A**) Comparisons of RAR between leukemic transformation patients and non-leukemic transformation patients. (**B**) Comparisons of RAR between survivors and non-survivors. (**C**) Distribution of RAR across DIPSS risk category. (**D**) Distribution of RAR across DIPSS-plus risk category.

RCS analysis further suggested positive non-linear associations between the RAR and leukemic transformations (p overall < 0.001, p nonlinear = 0.0118) and overall survival (p overall < 0.001, p nonlinear = 0.0216) (Figure 3C and D). In patients whose RAR was greater than the median value (RAR = 4.56), the HR for survival with per SD increase in the RAR was 1.45 (95% CI = 1.21–1.74).

ROC analysis was performed to further demonstrate the predictive ability of RAR for short-term and long-term OS in MF. The AUC values were 0.73 and 0.69 at the 1-year and 5-year time points, respectively, with the corresponding optimal cut-off values of 5.49 and 4.79 (Supplementary Figure 1).

Interaction and Subgroup Analysis

Survival analyses were conducted across various subgroups to assess potential effect modifications (Figure 4). The significant association between the RAR and survival was further verified among all subgroups except for patients with

Table 2 Multivariate Cox Proportional Hazards Regressions for Overall Survival in PMF Patients

	HR	95% CI	*p* value
Unadjusted model			
Categorical RAR			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.60	0.89–2.85	0.114
Tertile 3	5.06	3.03–8.46	< 0.001
p trend			< 0.001
Continuous RAR (per unit increase)	1.48	1.34–1.63	< 0.001
Continuous RAR (per SD increase)	1.73	1.51–1.99	< 0.001
Model 1: RAR + Age +Sex			
Categorical RAR			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.34	0.75–2.40	0.323
Tertile 3	4.40	2.62–7.39	< 0.001
p trend			< 0.001
Continuous RAR (per unit increase)	1.44	1.30–1.60	< 0.001
Continuous RAR (per SD increase)	1.67	1.45–1.93	< 0.001
Model 2: RAR + DIPSS Category			
Categorical RAR			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.18	0.65–2.15	0.555
Tertile 3	3.65	2.13–6.24	< 0.001
p trend			< 0.001
Continuous RAR (per unit increase)	1.43	1.29–1.59	< 0.001
Continuous RAR (per SD increase)	1.66	1.43–1.92	< 0.001
Model 3: RAR + DIPSS plus Category			
Categorical RAR			
Tertile 1	Reference	Reference	Reference
Tertile 2	1.12	0.62–2.03	0.697
Tertile 3	3.05	1.78–5.24	< 0.001
p trend			< 0.001
Continuous RAR (per unit increase)	1.39	1.24–1.55	< 0.001
Continuous RAR (per SD increase)	1.58	1.36–1.85	< 0.001

Abbreviations: PMF, primary myelofibrosis; HR, hazard ratio; RAR, red cell distribution width-to-albumin ratio.

PBB ≥ 1% (HR = 1.17, 95% CI = 0.99–1.38, $p = 0.060$). Intriguingly, transfusion dependence and PBB were identified as significant effect modifiers, with *p* interaction values of 0.004 and 0.006, respectively. The positive association between a high RAR and mortality was more pronounced in patients without transfusion dependence (HR = 1.55, 95% CI = 1.37–1.76) and patients with PBB < 1% (HR = 1.56, 95% CI = 1.40–1.75). In contrast, this relationship was attenuated in patients with transfusion dependence (HR = 1.17, 95% CI = 1.01–1.35).

Incremental Predictive Values of RAR

Table 3 demonstrates the incremental value of RAR for the prediction of OS. The integration of RAR into the DIPSS score significantly increased the discriminative ability, as indicated by the C-index (0.739 [95% CI: 0.686–0.792] vs 0.663 [95% CI: 0.610–0.716]). Similarly, adding RAR into the DIPSS-plus score significantly increased the C-index

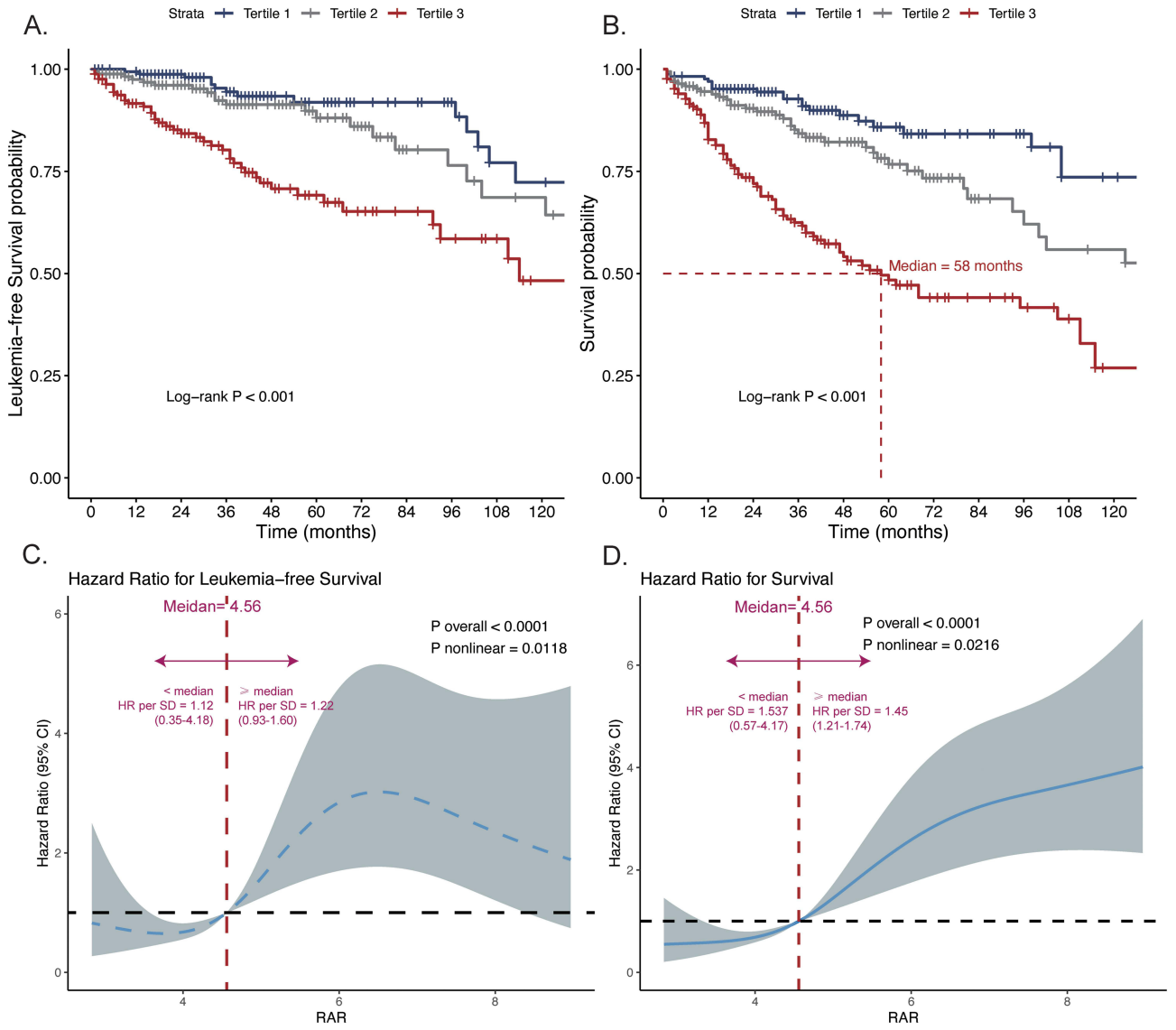

Figure 3 The associations between the RAR and overall survival.
Notes: (**A**) LFS estimated using the Kaplan–Meier method across RAR tertiles. (**B**) OS estimated using the Kaplan–Meier method across RAR tertiles. (**C**) RCS analysis for LFS. (**D**) RCS analysis for OS.

(0.762 [95% CI: 0.717–0.807] vs 0.709 [95% CI: 0.664–0.754]). The reclassification results improved significantly after adding a continuous RAR to DIPSS-plus score, with the cNRI increasing by 31.1% (95% CI: 9.6%–43.4%, $p = 0.004$) and the IDI increasing by 6.8% (95% CI: 2.3%–12.5%, $p < 0.001$) (Table 3). Additionally, the goodness of fit was assessed via the L-R test and the values of the AIC and BIC. The results of the L-R tests revealed that, compared with the DIPSS score or DIPSS-plus score alone, the addition of the RAR, whether in the form of a continuous variable or categorical variable, significantly improved model goodness of fit ($p < 0.001$ for all). Moreover, after adding RAR to the two prognostic scores, the absolute values of the AIC and BIC decreased.

A simplified summary comparing the C-index improvement across models is provided in Supplementary Table 1 to highlight the incremental value of RAR.

Construction of a Nomogram Based on RAR

Combining RAR and DIPSS-plus, we constructed an enhanced nomogram to predict 10-year survival in MF patients (Figure 5A). The coefficients of the RAR and DIPSS-plus scores were scaled and transformed into points based on their

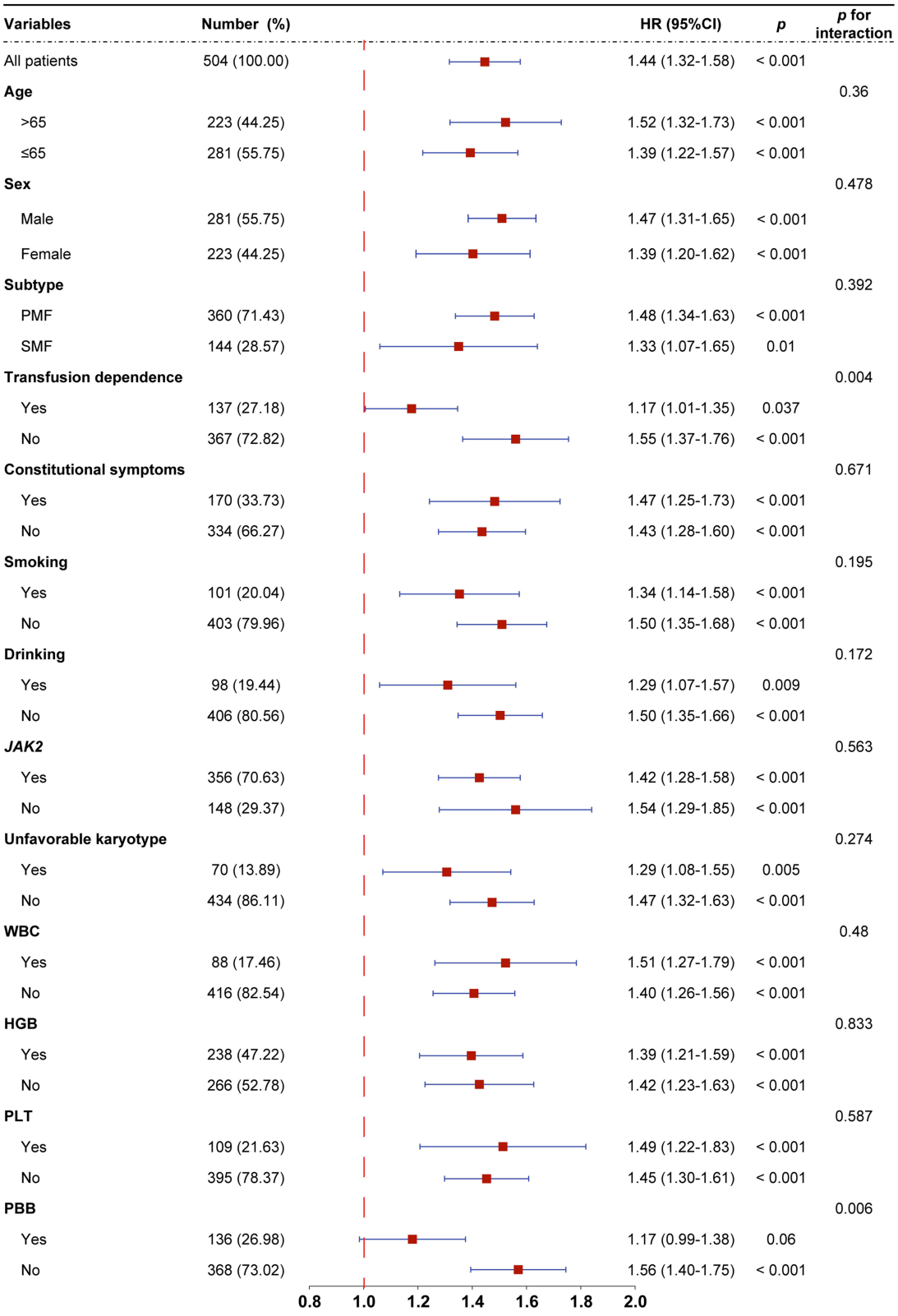

Figure 4 Subgroup analyses of RAR predicting overall survival.

https://doi.org/10.2147/JIR.S527476

Table 3 Enhancements of Model Performance for Overall Survival Through Integration of RAR

	Discrimination						Calibration		
	C-index	p	cNRI	p	IDI	p	L-R test, p	AIC	BIC
DIPSS	0.663	Reference	Reference	Reference	Reference	Reference	Reference	1112.04	1114.76
DIPSS + Categorical RAR	0.733	0.001	0.305 (0.113–0.439)	0.002	0.090 (0.033–0.159)	< 0.001	< 0.001	1079.75	1085.20
DIPSS + Continuous RAR	0.739	< 0.001	0.315 (0.147–0.432)	< 0.001	0.095 (0.046–0.154)	< 0.001	< 0.001	1075.76	1081.21
DIPSS-plus	0.709	Reference	Reference	Reference	Reference	Reference	Reference	1086.40	1089.13
DIPSS plus+ Categorical RAR	0.757	< 0.001	0.235 (0.104–0.399)	0.014	0.057 (0.014–0.124)	0.004	< 0.001	1064.87	1070.33
DIPSS plus + Continuous RAR	0.762	< 0.001	0.311 (0.096–0.434)	0.004	0.068 (0.023–0.125)	< 0.001	< 0.001	1060.00	1065.44

Abbreviations: RAR, red cell distribution width-to-albumin ratio; NRI, net reclassification improvement; IDI, integrated discrimination improvement; L-R test, likelihood-ratio test; AIC, Akaike information criterion; BIC, Bayesian information criterion.

relative significance in the nomogram. The total points were calculated by adding the individual scores. Patients with a total point ≥88 points were identified as high risk, whereas those with a total point <88 points were identified as low risk. The K-M method revealed a significant difference between the two categories ($p < 0.001$), suggesting the model's ability to effectively identify high-risk individuals (Figure 5B). The C-index of the model was 0.762 (95% CI: 0.717–0.807), which showed an improvement compared to DIPSS-plus alone (0.709, 95% CI: 0.664–0.754), indicating that the model had superior predictive accuracy (Figure 5C). In the calibration plot for adding the RAR into the DIPSS-Plus score, the observed line closely aligned with the diagonal reference line, indicating good model calibration (Figure 5D).

Discussion

Building on prior evidence, we hypothesized and confirmed that RAR provides significant prognostic value for clinical outcomes in patients with MF. To our knowledge, this is the first study to explore such a simple, two-parameter biomarker that integrates information on impaired erythropoiesis and malnutrition for prognostic value in MF. We demonstrated that RAR is independently associated with both LFS and OS, and its inclusion provided incremental prognostic value to traditional prognostic scores.

ROC analysis demonstrates moderate predictive power of RAR for predicting OS in MF. Notably, a baseline RAR exceeding 5.49 was associated with a higher risk of short-term death, while RAR exceeding 4.79 indicated a higher risk of long-term death, further supporting the clinical utility of RAR as a prognostic biomarker. Notably, the nomogram we developed, which integrates RAR into the DIPSS-plus framework, significantly improved predictive accuracy while maintaining simplicity, making it particularly useful in resource-limited settings. Our study underscoring the utility of RAR as a promising and cost-effective option to refine the risk stratification in MF patients, especially in those without transfusion dependence and PBB < 1%. Importantly, this study was conducted in a multicenter cohort over a 10-year period, which expands the generalizability and robustness of our findings.

Elevated RDW has been identified as a significant predictor of disease progression, such as the transformation of ET to post-ET MF.[24] Beyond its role in reflecting the variability in erythrocyte volume, a characteristic feature of MF, RDW has been correlated with increased levels of inflammatory biomarkers, such as C-reactive protein (CRP), IL-6, and the erythrocyte sedimentation rate in cancer patients.[25] This connection suggests that RDW is a surrogate indicator of chronic inflammation, which plays a central role in MF pathogenesis.[26] The possible mechanism is that *JAK2* V617F and other driver mutations lead to aberrant activation of the JAK-STAT signaling pathway, resulting in the excessive release of proinflammatory cytokines and inflammation in the bone marrow microenvironment.[27] These inflammatory responses disrupt erythropoiesis by suppressing erythropoietin activity and contribute to variability in erythrocyte volume.[28] Together, these findings prove that RDW could serve as a potential biomarker reflecting the severity and prognosis of MF.

Hypoproteinemia is associated with poor prognosis in the general population and is a well-established biomarker resulting from and reflecting malnutrition and the inflammatory response.[29,30] Albumin levels have been demonstrated to indicate a systemic inflammatory response, as the serum albumin concentration inversely decreases when the CRP level

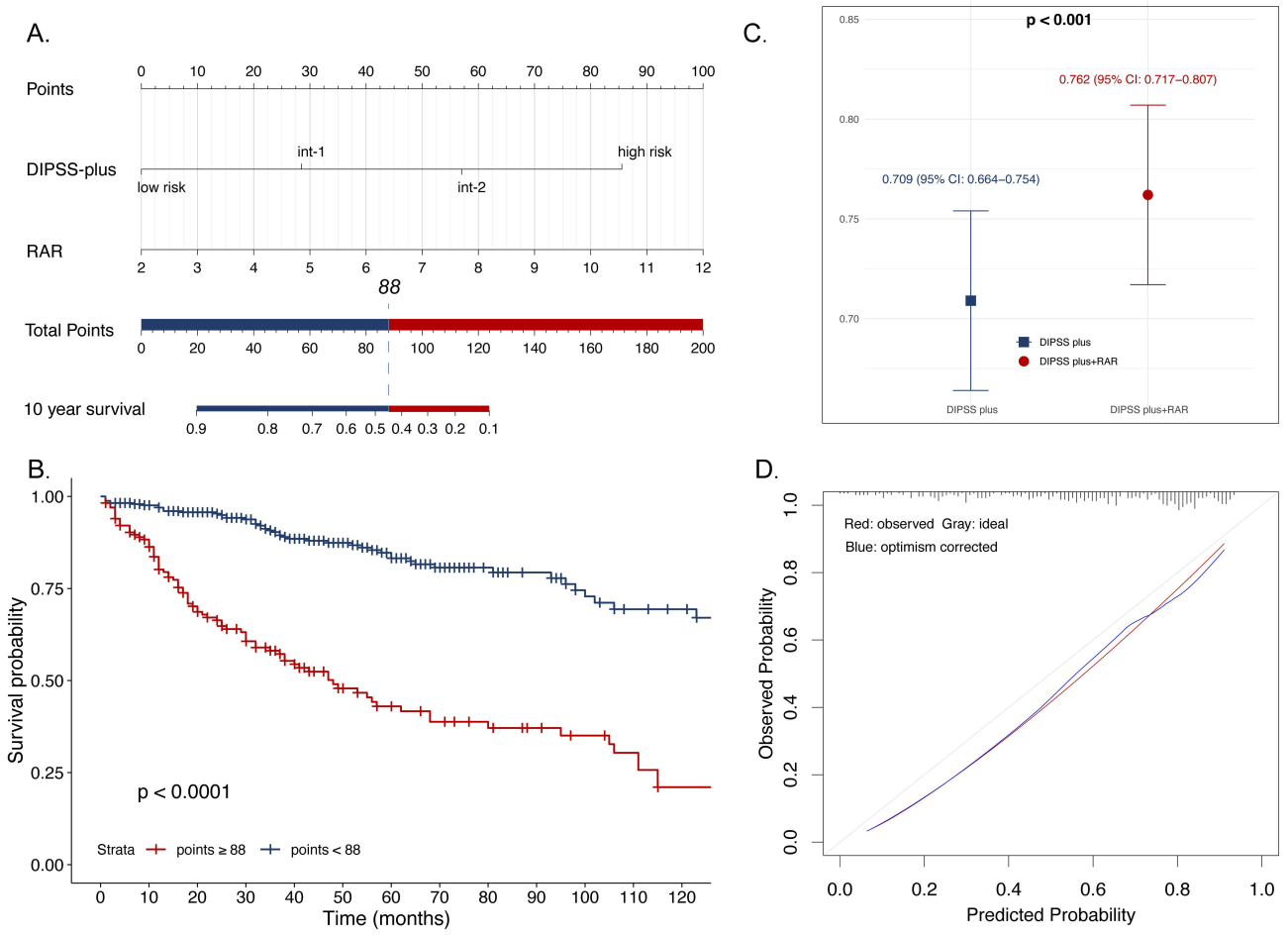

Figure 5 The incremental value of RAR to DIPSS-plus score.
Notes: (**A**) A nomogram. (**B**) OS estimated using the Kaplan–Meier method in patients with total points ≥88 and total points <88. (**C**) Parallel comparisons of C-indexes. (**D**) A calibration plot of the nomogram.

increases.[31] Additionally, the interplay between inflammation and nutrition is increasingly recognized as bidirectional and complex.[32] Inflammation modulates the effects of nutritional status, and the latter also significantly influences the body's inflammatory response. Notably, studies have demonstrated that albumin levels increase in response to the anti-inflammatory effects of ruxolitinib treatment, further underscoring its association with inflammation.[33]

MF involves a significantly shortened life expectancy with a heterogeneous OS,[34] and risk stratification can be achieved with different prognostic scoring systems on the basis of age, constitutional symptoms, hematologic parameters, and molecular and cytogenetic profiles. However, inflammatory and nutritional markers are rarely included in these assessments. Previous studies have examined the associations of the RAR with mortality in various disease-specific populations, such as patients with acute myocardial infarction,[35] diabetes,[36] stroke,[37] and rheumatoid arthritis.[38] These studies focused on various disease-specific populations and revealed significant associations between the RAR and adverse outcomes. Compared with the results of previous studies, our study is the first to investigate the association between the RAR and mortality in the MF population. Because MF is a chronic malignancy that is characterized by constitutive inflammation and catabolism, and the approved MF treatments act through the downregulating of inflammatory pathways, it stands to reason that the RAR holds prognostic value. Our findings demonstrated that the RAR serves as an independent prognostic factor beyond DIPSS-plus, enhancing both the calibration and discrimination capabilities of mortality prediction. Furthermore, the nomogram, comprising the DIPSS-plus score and RAR, offers an intuitive and visual tool to predict 10-year survival in clinical practice. To further illustrate the potential clinical utility of our nomogram, we provide an example of applying the nomogram to a representative patient from our cohort in Supplementary Figure 2. By aligning each predictor with its corresponding point value and

https://doi.org/10.2147/JIR.S527476

summing them, clinicians are enabled to visually estimate the 10-year survival probability, thereby promoting individualized risk stratification.

Notably, in subgroup analyses, the association between the RAR and mortality was particularly pronounced in patients with PBB < 1% and those without transfusion dependence. This underscores the sensitivity of the RAR as a prognostic marker, even in lower-risk patient populations.

This study has several limitations that should be acknowledged. First, owing to the observational nature of this study, causality cannot be inferred for the observed associations between RAR and all-cause mortality. Second, RAR were assessed only at baseline, and dynamic changes were not explored in this study. Further studies with repeated RAR should be conducted to determine its trajectory, and our findings should be validated in the future. Third, owing to the limited sample size of patients who underwent next-generation sequencing, we were unable to evaluate the impact of RAR on more comprehensive prognostic systems, such as MIPSS70 and MIPSS70+ Version 2.0.[39,40] Nevertheless, as a noninvasive and cost-effective marker, the prognostic value of RAR remains noteworthy, especially in resource-limited settings. Additionally, treatment strategies were not accounted for in this study, which may have confounded the prognostic performance of RAR. Nevertheless, as a real-world study, the large and multicenter nature of this cohort may reflect the diversity of clinical practice. Importantly, RAR demonstrated consistent prognostic value across multiple subgroups, supporting its robustness regardless of treatment variations. Future prospective studies incorporating treatment-related factors are needed to validate these findings.

This large, multi-center cohort study is the first to reveal the prognostic significance of RAR in MF. The modified predictive model combining DIPSS-plus score and RAR enhances prognostic discrimination and calibration, providing a simple yet cost-effective tool for refined risk stratification, especially in resource-limited settings.

Abbreviations

MF, myelofibrosis; MPN, myeloproliferative neoplasm; RAR, red cell distribution width to albumin ratio; PMF, primary myelofibrosis; SMF, secondary myelofibrosis; ET, essential thrombocythemia; JAKis, JAK inhibitors; WBC, white blood cells; HGB, hemoglobin; PLT, platelets; PBB, peripheral blood blasts; RDW, Red cell distribution width; OS, overall survival; WHO, World Health Organization; CVRs, cardiovascular risk factors; IQRs, interquartile ranges; LFS, leukemia-free survival; RCS, restricted cubic splines; cNRI, continuous net reclassification improvement; IDI, integrated discrimination improvement; L-R, likelihood-ratio; AIC, the Akaike information criterion; BIC, the Bayesian information criterion.

Ethics Statement

This study was approved by the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University Institutional Review Board and was conducted in compliance with the Declaration of Helsinki. Written informed consent was waived due to the retrospective nature of the study and the use of anonymized data (2022, No492).

Acknowledgments

Tian Zeng, Zhikang Zheng, Honglan Qian, Lirong Liu, Xiaowei Shi and Yanping Shao are co-first authors for this study. We would like to thank the CML and MPN Cooperation Group of Zhejiang Hematology for their support in data sharing and multicenter coordination.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was funded by the Key R&D Program of Zhejiang (No. 2022C03137) and the Zhejiang Medical Association Clinical Medical Research Special Fund Project (No. 2022ZYC-D09).

Disclosure

The authors declare they have no conflicts of interest in this work.

References

1. Mascarenhas J, Gleitz HFE, Chifotides HT, et al. Biological drivers of clinical phenotype in myelofibrosis. *Leukemia*. 2023;37(2):255–264. doi:10.1038/s41375-022-01767-y
2. Verstovsek S, Mesa RA, Livingston RA, Hu W, Mascarenhas J. Ten years of treatment with ruxolitinib for myelofibrosis: a review of safety. *J Hematol Oncol*. 2023;16(1):82. doi:10.1186/s13045-023-01471-z
3. Ali H, Bacigalupo A. 2024 update on allogeneic hematopoietic stem cell transplant for myelofibrosis: a review of current data and applications on risk stratification and management. *Am J Hematol*. 2024;99(5):938–945. doi:10.1002/ajh.27274
4. Mesa RA, Li CY, Ketterling RP, Schroeder GS, Knudson RA, Tefferi A. Leukemic transformation in myelofibrosis with myeloid metaplasia: a single-institution experience with 91 cases. *Blood*. 2005;105(3):973–977. doi:10.1182/blood-2004-07-2864
5. Verstovsek S, Gotlib J, Mesa RA, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. *J Hematol Oncol*. 2017;10(1):156. doi:10.1186/s13045-017-0527-7
6. Chifotides HT, Bose P, Verstovsek S. Momelotinib: an emerging treatment for myelofibrosis patients with anemia. *J Hematol Oncol*. 2022;15(1):7. doi:10.1186/s13045-021-01157-4
7. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (international working group for myeloproliferative neoplasms research and treatment). *Blood*. 2010;115(9):1703–1708. doi:10.1182/blood-2009-09-245837
8. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined dynamic international prognostic scoring system for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol*. 2011;29(4):392–397. doi:10.1200/jco.2010.32.2446
9. Tefferi A, Lasho TL, Jimma T, et al. One thousand patients with primary myelofibrosis: the mayo clinic experience. *Mayo Clin Proc*. 2012;87(1):25–33. doi:10.1016/j.mayocp.2011.11.001
10. Tefferi A. Primary myelofibrosis: 2013 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2013;88(2):141–150. doi:10.1002/ajh.23384
11. May JE, Marques MB, Reddy VVB, Gangaraju R. Three neglected numbers in the CBC: the RDW, MPV, and NRBC count. *Cleve Clin J Med*. 2019;86(3):167–172. doi:10.3949/ccjm.86a.18072
12. Lucijanic M, Pejsa V, Jaksic O, et al. The degree of anisocytosis predicts survival in patients with primary myelofibrosis. *Acta Haematol*. 2016;136(2):98–100. doi:10.1159/000445247
13. Cattaneo D, Galli N, Bucelli C, et al. Red cell distribution width and prognosis in myelofibrosis patients treated with ruxolitinib. *Ann Hematol*. 2024;103(8):2787–2795. doi:10.1007/s00277-024-05801-0
14. Tefferi A, Nicolosi M, Penna D, et al. Development of a prognostically relevant cachexia index in primary myelofibrosis using serum albumin and cholesterol levels. *Blood Adv*. 2018;2(15):1980–1984. doi:10.1182/bloodadvances.2018018051
15. Kuykendall AT, Ball S, Mora B, et al. Investigation of serum albumin as a dynamic treatment-specific surrogate for outcomes in patients with myelofibrosis treated with ruxolitinib. *JCO Precis Oncol*. 2024;8:e2300593. doi:10.1200/po.23.00593
16. Hao M, Jiang S, Tang J, et al. Ratio of red blood cell distribution width to albumin level and risk of mortality. *JAMA Network Open*. 2024;7(5):e2413213. doi:10.1001/jamanetworkopen.2024.13213
17. Larsen MK, Skov V, Kjær L, et al. Neutrophil-to-lymphocyte ratio and all-cause mortality with and without myeloproliferative neoplasms-a Danish longitudinal study. *Blood Cancer J*. 2024;14(1):28. doi:10.1038/s41408-024-00994-z
18. Laganà A, Passucci M, Pepe S, et al. Neutrophil to lymphocyte ratio in myelofibrosis patients treated with ruxolitinib may predict prognosis and rate of discontinuation. *Eur J Haematol*. 2024;112(6):938–943. doi:10.1111/ejh.14188
19. Lucijanic M, Krecak I, Galusic D, et al. Triple a score (AAA: age, absolute neutrophil count and absolute lymphocyte count) and its prognostic utility in patients with overt fibrotic and prefibrotic myelofibrosis. *Ann Hematol*. 2024;103(6):2157–2159. doi:10.1007/s00277-024-05751-7
20. Lucijanic M, Cicic D, Stoos-Veic T, et al. Elevated neutrophil-to-lymphocyte-ratio and platelet-to-lymphocyte ratio in myelofibrosis: inflammatory biomarkers or representatives of myeloproliferation itself? *Anticancer Res*. 2018;38(5):3157–3163. doi:10.21873/anticanres.12579
21. Dingli S, Fathima S, Faldu P, Gangat N, Dingli D, Tefferi A. Basophilia and eosinophilia in primary myelofibrosis: phenotype, genotype, and prognostic correlates. *Blood Cancer J*. 2025;15(1):72. doi:10.1038/s41408-025-01285-x
22. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the world health organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. doi:10.1182/blood-2016-03-643544
23. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the international working group for myelofibrosis research and treatment. *Blood*. 2009;113(13):2895–2901. doi:10.1182/blood-2008-07-170449
24. Xiang D, Yang X, Qian H, et al. Development and validation of a model for the early prediction of progression from essential thrombocythemia to post-essential thrombocythemia myelofibrosis: a multicentre retrospective study. *EClinicalMedicine*. 2024;67:102378. doi:10.1016/j.eclinm.2023.102378
25. Wang PF, Song SY, Guo H, Wang TJ, Liu N, Yan CX. Prognostic role of pretreatment red blood cell distribution width in patients with cancer: a meta-analysis of 49 studies. *J Cancer*. 2019;10(18):4305–4317. doi:10.7150/jca.31598
26. Hermouet S, Bigot-Corbel E, Gardie B. Pathogenesis of myeloproliferative neoplasms: role and mechanisms of chronic inflammation. *Mediators Inflamm*. 2015;2015:145293. doi:10.1155/2015/145293

27. Woods B, Chen W, Chiu S, et al. Activation of JAK/STAT signaling in megakaryocytes sustains myeloproliferation in vivo. *Clin Cancer Res*. 2019;25(19):5901–5912. doi:10.1158/1078-0432.Ccr-18-4089
28. Hong J, Zhu B, Cai X, et al. Assessment of the association between red blood cell distribution width and disease activity in patients with systemic vasculitis. *Exp Ther Med*. 2021;22(1):691. doi:10.3892/etm.2021.10123
29. Arques S. Human serum albumin in cardiovascular diseases. *Eur J Intern Med*. 2018;52:8–12. doi:10.1016/j.ejim.2018.04.014
30. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. *JPEN J Parenter Enteral Nutr*. 2019;43(2):181–193. doi:10.1002/jpen.1451
31. Allison SP, Lobo DN. The clinical significance of hypoalbuminaemia. *Clin Nutr*. 2024;43(4):909–914. doi:10.1016/j.clnu.2024.02.018
32. Stumpf F, Keller B, Gressies C, Schuetz P. Inflammation and nutrition: friend or foe? *Nutrients*. 2023;15(5). doi:10.3390/nu15051159
33. Mesa RA, Verstovsek S, Gupta V, et al. Effects of ruxolitinib treatment on metabolic and nutritional parameters in patients with myelofibrosis from COMFORT-I. *Clin Lymphoma Myeloma Leuk*. 2015;15(4):214–221.e1. doi:10.1016/j.clml.2014.12.008
34. Masarova L, Bose P, Pemmaraju N, et al. Improved survival of patients with myelofibrosis in the last decade: single-center experience. *Cancer*. 2022;128(8):1658–1665. doi:10.1002/cncr.34103
35. Ruan L, Xu S, Qin Y, et al. Red blood cell distribution width to albumin ratio for predicting type i cardiorenal syndrome in patients with acute myocardial infarction: a retrospective cohort study. *J Inflamm Res*. 2024;17:3771–3784. doi:10.2147/jir.S454904
36. Yu M, Pei L, Liu H, et al. A novel inflammatory marker: relationship between red cell distribution width/albumin ratio and vascular complications in patients with type 2 diabetes mellitus. *J Inflamm Res*. 2024;17:6265–6276. doi:10.2147/jir.S476048
37. Ding T, Hu X, Shao L, et al. The radio of RDW/ALB: a cost-effective biomarker for early-stage risk stratification in acute ischemic stroke. *Int J Gen Med*. 2024;17:4407–4418. doi:10.2147/ijgm.S486495
38. Zhang C, Lu S, Kang T, et al. Red cell distribution width/albumin ratio and mortality risk in rheumatoid arthritis patients: insights from a NHANES study. *Int J Rheum Dis*. 2024;27(9):e15335. doi:10.1111/1756-185x.15335
39. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: mutation-enhanced international prognostic score system for transplantation-age patients with primary myelofibrosis. *J Clin Oncol*. 2018;36(4):310–318. doi:10.1200/jco.2017.76.4886
40. Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70+ version 2.0: mutation and karyotype-enhanced international prognostic scoring system for primary myelofibrosis. *J Clin Oncol*. 2018;36(17):1769–1770. doi:10.1200/jco.2018.78.9867