Blood and Lymphatic Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Albumin-to-Globulin Ratio Combined with Neutrophil-to-Lymphocyte Ratio as a Prognostic Predictor in Multiple Myeloma with Renal Impairment

Yingzi Zhang[1], Xiajuan Yao[1], Yaoquan Zhang[1], Zhuyun Chen[1], Zhongke Qin[1], Ying Cai[2], Wenkai Xia[1], Hong Hu[1]

[1]Department of Nephrology, Jiangyin People's Hospital Affiliated to Nantong University, Jiangyin, Jiangsu, 214400, People's Republic of China; [2]Department of Hematology, Jiangyin People's Hospital Affiliated to Nantong University, Jiangyin, Jiangsu, 214400, People's Republic of China

Correspondence: Wenkai Xia; Hong Hu, Department of Nephrology, Jiangyin People's Hospital Affiliated to Nantong University, 3 Yingrui Road, Jiangyin, Jiangsu, 214400, People's Republic of China, Email xiawenkai.xia@gmail.com; huhong1523@163.com

Background: The albumin-to-globulin ratio (AGR) and neutrophil-to-lymphocyte ratio (NLR) have been recently regarded as promising prognostic factors in various malignancies. The present study investigated the prognostic value of combining the AGR and NLR (ANS) for risk assessments in multiple myeloma (MM) with renal impairment (RI).

Methods: From 2011 to 2018, 79 patients with MM and RI were enrolled in this study. Receiver operating curves (ROCs) were constructed to determine optimal AGR and NLR thresholds for predicting overall survival (OS) and progression-free survival (PFS) during follow up. The prognostic values of AGR, NLR, and ANS were evaluated with Cox regression and Kaplan-Meier methods. We also created a predictive nomogram for prognostic evaluations of OS and PFS, and the predictive accuracy was assessed with a concordance index (c-index).

Results: The ROC curves analyses showed that the optimal cut-off levels were 2.27 for NLR and 1.57 for AGR. A high NLR and a high ANS were significantly associated with worse OS and PFS. However, a high NLR combined with a low AGR was associated with worse OS. Multivariate analyses demonstrated that both the NLR and ANS were independent predictors for both OS and PFS and that a low AGR was an independent predictor of a reduced OS. The nomogram accurately predicted OS (c-index: 0.785) and PFS (c-index: 0.786) in patients with MM and RI.

Conclusion: ANS may serve as a potential prognostic biomarker in patients with MM and RI. The proposed nomograms may facilitate prognostic predictions for patients with MM and RI.

Keywords: multiple myeloma, renal impairment, neutrophil–lymphocyte ratio, albumin-to-globulin ratio, prognosis

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy after lymphoma. MM accounts for 1% of all cancers worldwide.[1] Renal impairment (RI) is a common manifestation of MM, and renal dysfunction may be associated with increased mortality risk. Despite improvements in MM treatments over the past few decades, the presence of RI restricts therapeutic options and eligibility for autologous stem cell transplantation.[2] Therefore, it is necessary to understand the risk factors associated with MM progression and deterioration and to identify potentially useful biomarkers for predicting patient prognosis. Several conventional prognostic factors have been included in different MM staging systems, such as the Durie-Salmon Staging System, the International Staging System and (ISS), and the Revised International Staging System.[3,4] However, patients with high risk have heterogeneous outcomes.[5,6] Therefore, other potential biomarkers should be systematically investigated and developed as complementary tools to improve patient management.

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The peripheral blood neutrophil-to-lymphocyte ratio (NLR) has been recognized as an important indicator of the systemic inflammatory response. Moreover, increasing evidence has revealed that the NLR could play an important role in predicting the prognosis of patients with different types of solid tumors[7–9] and other diseases, including atherosclerosis[10] and systemic lupus erythematosus.[11] Similarly, the albumin-to-globulin ratio (AGR) was frequently reported as a simple, valuable biomarker for evaluating several diseases, including chronic kidney disease,[12] stroke,[13] and heart failure.[14] Recently, new applications have been discovered for NLR and AGR as prognostic factors in hematological malignancies, mostly lymphomas and leukemias.[15,16] However, MM patients with RI frequently presented with advanced disease and high tumor burden at diagnosis, they will typically have low albumin and high globulin which may make the AGR as a surrogate for advanced disease or worsening renal injury. Moreover, the prognostic value of combined NLR and AGR is relatively limited in MM patients with RI. The present study aimed to investigate and compare the impacts of AGR, NLR, and the combination of AGR and NLR (ANS) on the survival and prognosis of patients with MM and RI.

Materials and Methods

Patients

This single-center retrospective study analyzed the medical records of 200 Patients newly diagnosed with MM between January 2011 and December 2018 at Jiangyin People's Hospital Affiliated to Nantong University. Among 97 patients with RI, 12 were excluded due to active infections or chronic inflammation. In addition, 6 patients were excluded, due to liver cirrhosis, rheumatic disease, or other autoimmune diseases recorded at the initial diagnosis. Finally, 79 patients were enrolled in the study (Figure 1). Kidney function was assessed with the estimated glomerular filtration rate (eGFR), determined with the simplified 4-variable equation from the Modification of Diet in Renal Disease study.[17] The definition of renal impairment was an eGFR less than 60mL/min/1.72m^2 at initial diagnosis. Oliguria was defined as urine output less than 0.5mL/kg/hours for 6 hours or more at initial diagnosis.[17] The degree of renal function recovery was assessed using proposed criteria.[18] Complete renal response was defined as a sustained improvement in baseline eGFR of > 60mL/min/1.73m^2. Partial renal response was defined as an increase in eGFR from <15 to 30–59 mL/min/1.73m^2, and minor renal response was defined as a sustained increase in eGFR from <15 mL/min to 15–29 mL/min. Overall survival (OS) was calculated from the date of diagnosis to death or censoring on 31 Dec 2018. Progression-free survival (PFS) was calculated from the start of first-line treatment to disease relapse or last follow-up. The study was approved by the Medical Ethics Committee of Jiangyin People's Hospital Affiliated to Nantong University and complied with the Declaration of Helsinki. Informed consent was waived by the Ethics Committee, due to the retrospective and non-interventional nature of the study.

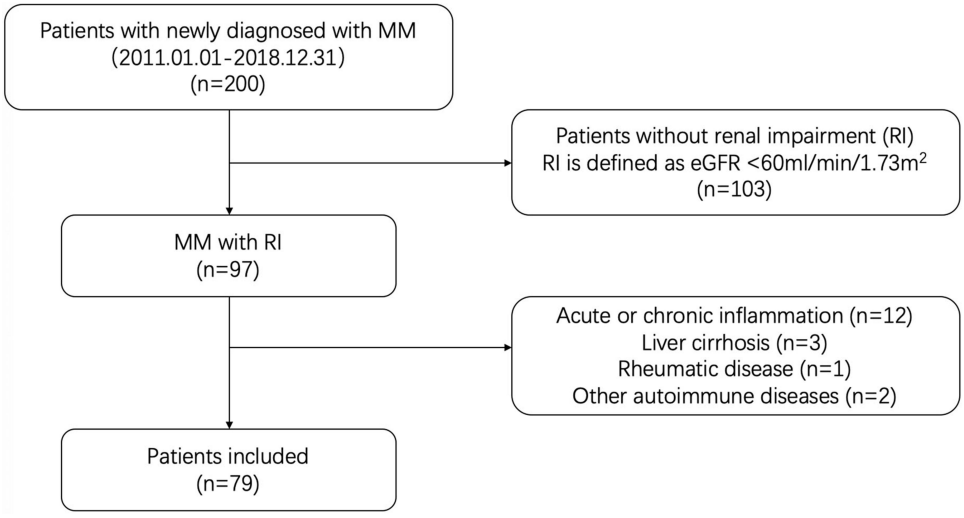

Figure 1 Enrollment flowchart for analysis.

Medical and Laboratory Data Collection

Peripheral blood was collected to measure laboratory values at initial diagnosis, including the levels of hemoglobin, red blood cells, white blood cells, immunoglobulin, albumin, globulin, and platelets. The NLR was defined as the neutrophil count divided by the lymphocyte count. The AGR was defined as the albumin concentration divided by the total protein concentration minus the albumin concentration. High and low ratios were defined by cut-off values on receiver operating curves (ROCs) (Figure 2). ANS was defined as the combination of decreased AGR and increased NLR. The ANS was scored based on whether each ratio indicated a favorable or unfavorable outcome. For example, an ANS of 2 indicated that both ratios were unfavorable (ie, AGR <1.57 and NLR ≥2.27); an ANS of 1 indicated only one unfavorable ratio (AGR <1.57 or NLR ≥2.27); and an ANS of 0 indicated that both ratios were favorable (AGR≥1.57 and NLR <2.27).

Statistical Analysis

We determined optimal cut-off values for the NLR and AGR with ROC analyses, based on associations with the main endpoint, the OS. Subsequently, patients were divided into two groups according to the optimal cutoff values of NLR and AGR, respectively. Categorical variables were compared with Chi-square test, Fisher's exact test, or a one-way analysis of variance (ANOVA), as appropriate. Continuous variables were compared with the Mann–Whitney U or Kruskal–Wallis test. Survival rates were evaluated with the Kaplan-Meier method, and differences were assessed with the Log rank test. Variables that were potential predictors of OS and PFS in the univariate analysis were included in a Cox proportional hazards regression model for multivariable analysis. The nomogram and calibration curve were created with R 3.0.3 software, and predictive accuracy was evaluated with Harrell's concordance index (c-index). *P*-values <0.05 were considered statically significant. All statistical analyses were performed with IBM SPSS 20.0 software (IBM, USA).

Results

Comparison of Characteristics Between MM Patients with and without Renal Impairment

The general characteristics of MM patients with and without RI were shown in Table 1. When comparing MM patients with and without RI, no statistical difference was found in age, RDW, WBC and options of treatment (all P values

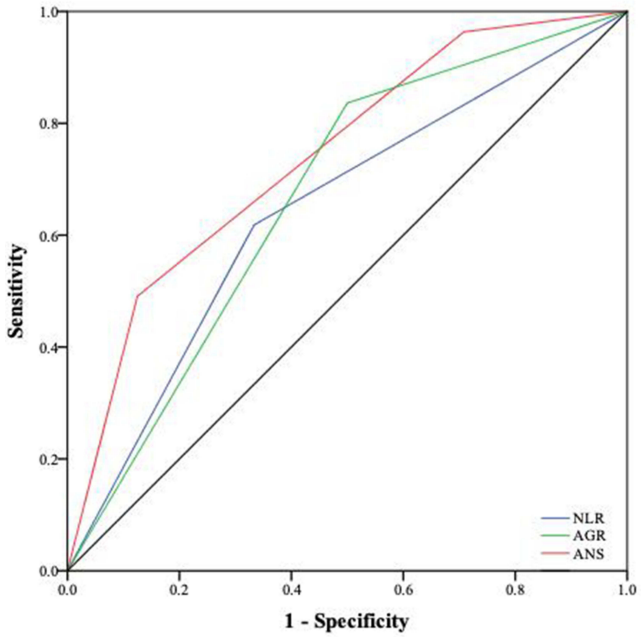

Figure 2 Predictive value of NLR, AGR and their combinations for all-cause mortality in MM patients with RI.

Table 1 Characteristics of MM Patients with and without Renal Impairment

Characteristics	MM with RI (n=79)	MM without RI (n=116)	*P*
Age	66±10	65±9	0.624
Gender n (%)			<0.001
Male	57 (72.2)	56 (48.3)	
Hb (g/L)	78.7±19.5	98.3±23.0	<0.001
RBC (10^{12}/L)	2.6±0.6	3.2±0.7	<0.001
RDW (%)	14.7±2.2	15.3±2.8	0.158
WBC (10^9/L)	5.4±2.9	5.0±2.4	0.263
Platelet (10^9/L)	143.5±77.8	164.6±69.3	0.045
NLR	2.6±1.7	2.6±2.3	0.847
AGR	1.1±0.7	0.8±0.6	0.024
β2 microglobulin (mg/L)	11.6±7.7	4.3±2.8	<0.001
ECOG			<0.001
1–2	60 (75.9)	55 (47.4)	
3–4	19 (24.1)	61 (52.6)	
M protein type (%)			<0.001
Ig G	28 (35.4)	57 (49.1)	
Ig A	14 (17.7)	39 (33.6)	
Ig M	0 (0)	1 (0.9)	
Light chain (L)	29 (36.7)	11 (9.5)	
Light chain (K)	6 (7.6)	6 (5.2)	
Ig D	2 (2.5)	2 (1.7)	
ISS Stage n (%)			<0.001
I	5 (6.3)	20 (17.2)	
II	19 (24.1)	69 (59.5)	
III	55 (69.6)	27 (23.3)	
Treatment n (%)			0.185
Chemotherapy	76 (96.2)	110 (94.8)	
Stem cell transplant	3 (3.8)	6 (5.2)	

Abbreviations: AGR, Albumin-globulin ratio; NLR, neutrophil-lymphocyte ratio; Hb, hemoglobin; RBC, red blood count; RDW, red cell distribution width; WBC, white blood count; ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group performance status.

>0.05). Meanwhile, patients with RI were more likely to be male and presented with anemia, as well as higher values of β2 microglobulin and ISS stage. The AGR level in MM patients with RI was significantly higher than those without RI. However, no statistically difference was observed in NLR between two groups.

Optimal Thresholds for NLR and AGR

The optimal cutoff values for NLR and AGR were determined with receiver operating curve (ROC) analyses. According to the highest Youden's index, the optimal cutoff points were 2.27 (AUC: 0.563, 95% CI: 0.424–0.702, *P*=0.003) for NLR and 1.57 (AUC: 0.688, 95% CI: 0.567–0.720, *P*=0.008) for AGR. When we combined the AGR and NLR to obtain the ANS score, the three score categories exhibited better predictive value (AUC: 0.741, 95% CI: 0.623–0.860, *P*=0.001) than either the AGR or NLR alone.

Relationship Between NLR, AGR and Clinicopathologic Data in MM Patients with Renal Impairment

A total of 79 MM patients with RI were divided into a high group and a low group based on the optimal cutoff values of NLR and AGR, and the clinical and biochemical characteristics of the two groups were compared and shown in Tables 2 and 3. It

Table 2 Baseline Characteristics According to NLR

Characteristics	NLR< 2.27 (n=37)	NLR≥ 2.27 (n=42)	*P*
Age	66±10	64±10	0.452
Gender n (%)			0.097
Male	30 (81.1)	27 (64.3)	
Hb (g/L)	76.34±21.80	80.68±17.85	0.335
RBC (10^{12}/L)	2.49±0.71	2.63±0.61	0.345
RDW (%)	14.20 (13.45, 16.60)	13.95 (13.10, 14.55)	0.069
WBC (10^9/L)	4.28 (3.42, 5.40)	5.51 (3.73, 7.30)	0.012
ANC (10^9/L)	2.19 (1.52, 2.28)	3.96 (2.56, 5.17)	0.000
ALC (10^9/L)	1.73±0.73	1.23±0.60	0.001
Platelet (10^9/L)	112.00 (85.00, 153.50)	148.50 (90.75, 216.75)	0.031
Albumin (g/L)	34.33±5.89	35.15±6.45	0.560
Globulin (g/L)	49.80 (26.45, 77.85)	32.80 (22.53, 64.85)	0.084
Urea (mmol/L)	11.50 (8.03, 17.18)	9.90 (7.20,12.43)	0.236
Creatine (umol/L)	165.40 (130.30, 362.95)	324.05 (174.10, 696.60)	0.001
β2 microglobulin (mg/L)	7.93 (5.53, 18.97)	10.22 (5.87, 20.76)	0.655
ECOG			0.635
1–2	29 (78.4)	31 (73.8)	
3–4	8 (21.6)	11 (26.2)	
eGFR (mL/min*1.73 m^2)	40.30 (18.45, 58.65)	19.55 (8.98, 40.58)	0.002
M protein type (%)			0.787
Ig G	14 (37.8)	14 (33.3)	
Ig A	7 (18.9)	7 (16.7)	
Ig M	0 (0)	0 (0)	
Light chain (L)	14 (37.8)	15 (35.7)	
Light chain (K)	2 (5.4)	4 (9.5)	
Ig D	0 (0)	2 (4.8)	
ISS Stage n (%)			0.407
I	1 (2.7)	4 (9.5)	
II	8 (21.6)	11 (26.2)	
III	28 (75.7)	27 (64.2)	
Treatment n (%)			0.243
Chemotherapy	37 (100)	39 (92.9)	
Stem cell transplant	0 (0)	3 (7.1)	

Abbreviations: AGR, Albumin-globulin ratio; NLR, neutrophil-lymphocyte ratio; Hb, hemoglobin; RBC, red blood count; RDW, red cell distribution width; WBC, white blood count; ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group performance status.

was shown that higher NLR level was significantly associated with higher platelet, higher creatinine and lower eGFR. A comparison of high and low AGR groups showed that high AGR was significantly correlated with lower ANC, but not with other pathological parameters.

Correlations Between ANS Values and Patient Clinical-pathological Characteristics

The associations between ANS values and patient clinicopathologic characteristics are shown in Table 4. These Results revealed that ANS was significantly correlated with patient sex (P=0.035), the white blood cell count (P=0.024), the absolute neutrophil count (P=0.003), the albumin level (P=0.004), the globulin level (P=0.009), the NLR (P<0.001), and the AGR (P<0.001).

Table 3 Baseline Characteristics According to AGR

Characteristics	AGR<1.57 (n=58)	AGR≥1.57 (n=21)	*P*
Age	66±11	65±8	0.824
Gender n (%)			0.513
Male	43 (74.1)	14 (66.7)	
Hb (g/L)	78.18±20.95	79.93±16.52	0.731
RBC (10^{12}/L)	2.56±0.69	2.57±0.57	0.917
RDW (%)	14.15 (13.38, 15.50)	13.80 (13.30, 14.70)	0.289
WBC (10^9/L)	5.08 (3.56, 6.75)	5.02 (3.61, 5.59)	0.657
ANC (10^9/L)	2.84 (1.99, 4.14)	2.99 (2.28, 4.19)	0.579
ALC (10^9/L)	1.55±0.77	1.23±0.44	0024
Platelet (10^9/L)	121.50 (89.75, 184.00)	112.00 (87.00, 201.50)	0.912
Albumin (g/L)	33.00±5.57	39.65±5.10	0.000
Globulin (g/L)	51.45 (34.98, 76.63)	19.60 (17.85, 21.70)	0.000
Urea (mmol/L)	10.07 (8.06, 16.57)	10.00 (7.20, 14.36)	0.606
Creatine (umol/L)	219.40 (144.85, 405.05)	317.90 (131.65, 518.85)	0.464
β2 microglobulin (mg/L)	9.98 (5.67, 16.26)	11.37 (5.87, 23.06)	0.315
ECOG			0.976
1–2	44 (75.9)	16 (76.2)	
3–4	14 (24.1)	5 (23.8)	
eGFR (mL/min*1.73 m^2)	32.00 (15.50, 49.90)	21.70 (12.90, 57.10)	0.495
M protein type (%)			0.599
Ig G	22 (37.9)	6 (28.6)	
Ig A	10 (17.2)	4 (19.0)	
Ig M	0 (0)	0 (0)	
Light chain (L)	21 (36.2)	8 (38.1)	
Light chain (K)	3 (5.2)	3 (14.3)	
Ig D	2 (3.4)	0 (0)	
ISS Stage n (%)			0.622
I	3 (5.2)	2 (9.5)	
II	13 (22.4)	6 (28.6)	
III	42 (72.4)	13 (61.9)	
Treatment n (%)			0.787
Chemotherapy	56 (96.6)	20 (95.2)	
Stem cell transplant	2 (3.4)	1 (4.8)	

Abbreviations: AGR, Albumin-globulin ratio; NLR, neutrophil-lymphocyte ratio; Hb, hemoglobin; RBC, red blood count; RDW, red cell distribution width; WBC, white blood count; ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group performance status.

Table 4 Correlation of ANS with the Clinicopathological Characteristics of the MM Patients with RI

Characteristics	ANS=0 (n=9)	ANS=1 (n=40)	ANS=2 (n=30)	*P*
Age	67±6	65±10	65±11	0.905
Gender n (%)				0.035
Male	5 (55.6)	34 (85.0)	18 (60.0)	
Hb (g/L)	74.64±13.77	79.00±22.34	79.39±17.99	0.813
RBC (10^{12}/L)	2.34±0.46	2.60±0.73	2.58±0.61	0.550
RDW (%)	13.60 (13.25, 14.70)	14.35 (13.43, 16.18)	13.95 (12.95, 14.55)	0.248
WBC (10^9/L)	4.25 (3.61, 5.03)	4.92 (3.30, 6.27)	5.58 (3.73, 7.75)	0.024
ANC (10^9/L)	2.42 (1.95, 2.87)	2.45 (1.64, 3.85)	3.92 (2.56, 5.15)	0.003
ALC (10^9/L)	1.42±0.33	1.61±0.79	1.29±0.65	0.167

(*Continued*)

Table 4 (Continued).

Characteristics	ANS=0 (n=9)	ANS=1 (n=40)	ANS=2 (n=30)	*P*
Platelet (10^9/L)	112.00 (74.00, 159.50)	113.50 (88.00, 156.25)	152.50 (90.75, 216.75)	0.418
Albumin (g/L)	40.99±3.61	34.13±5.89	33.75±6.20	0.004
Globulin (g/L)	20.40 (18.00,21.70)	46.00 (29.55, 37.10)	44.05 (30.20,68.10)	0.009
Urea (mmol/L)	11.76 (7.65, 16.13)	10.10 (7.38, 16.14)	9.90 (7.48, 12.23)	0.951
Creatine (umol/L)	303.70 (127.95, 439.85)	173.30 (130.75, 410.13)	315.55 (190.33, 696.60)	0.086
β2 microglobulin (mg/L)	7.93 (5.53, 21.14)	10.18 (5.74, 19.92)	10.12 (5.95, 14.55)	0.880
ECOG				0.579
1–2	8 (88.9)	29 (72.5)	23 (76.7)	
3–4	1 (11.1)	11 (27.5)	7 (23.3)	
eGFR (mL/min*1.73 m^2)	23.10 (15.65, 57.20)	39.85 (16.35, 58.50)	19.55 (9.43, 38.90)	0.062
M protein type (%)				
Ig G	4 (44.4)	12 (30.0)	12 (40.0)	
Ig A	0 (0)	11 (27.5)	3 (10)	
Ig M	0 (0)	0 (0)	0 (0)	
Light chain (L)	5 (55.6)	12 (30.0)	12 (40)	
Light chain (K)	0 (0)	5 (12.5)	1 (3.3)	
Ig D	0 (0)	0 (0)	2 (6.7)	
ISS Stage n (%)				0.052
I	3 (33.3)	1 (2.5)	1 (3.3)	
II	1 (11.1)	9 (22.5)	9 (30.0)	
III	5 (55.6)	30 (75.0)	20 (66.7)	
Treatment n (%)				0.767
Chemotherapy	9 (100)	38 (95.0)	29 (96.7)	
Stem cell transplant	0 (0)	2 (5.0)	1 (3.3)	
NLR	1.75±0.53	2.15±1.50	3.77±1.84	0.000
AGR	2.19±0.70	1.04±0.74	0.82±0.41	0.000

Abbreviations: AGR, Albumin-globulin ratio; NLR, neutrophil-lymphocyte ratio; Hb, hemoglobin; RBC, red blood count; RDW, red cell distribution width; WBC, white blood count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; eGFR, estimated glomerular filtration rate; ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group performance status.

Associations Between the NLR, AGR, and ANS and Clinical Prognosis

Kaplan -Meier survival analyses and Log rank tests were performed to determine how NLR, AGR, and ANS were associated with patient outcomes. Our results revealed that NLR values ≥2. 27 were significantly associated with reduced OS and PFS, and that AGR values <1.57 were associated with reduced OS (Figures 1 and 2). In addition, we observed a significant relationship between the ANS and the clinical prognosis (OS and PFS; Figures 3 and 4).

The variables that showed significant clinicopathological associations in the univariate analysis were included in a multivariate analysis to perform further evaluations of their influences on OS and PFS. Our results revealed that Eastern Cooperative Oncology Group performance status scores of 3 and 4 and eGFR values <50.5 mL/min were significantly associated with reduced OS and PFS (P_{all} <0.01; Table 5). Additionally, unfavorable survival rates were associated with elevations in the NLR (HR=1.82, 95% CI: 1.02–3.28, *P*=0.044 for OS and HR=2.34, 95% CI: 1.42–3.85, *P*=0.001 for PFS) and the ANS (HR=2.25, 95% CI: 1.42–3.58, *P*=0.001 for OS and HR=1.54, 95% CI: 1.01–2.34, *P*=0.044 for PFS). We also found that β2 microglobulin (HR=2.58, 95% CI: 1.33–5.02, *P*=0.005) and AGR (HR=0.33, 95% CI: 0.16–0.68, *P*=0.003) were independently associated with OS. Importantly, a high eGFR was identified as an independent indicator of favorable outcomes (HR=0.35, 95% CI: 0.16–0.77, *P*=0.010 for OS and HR=0.54, 95% CI: 0.30–0.94, *P*=0.031 for PFS).

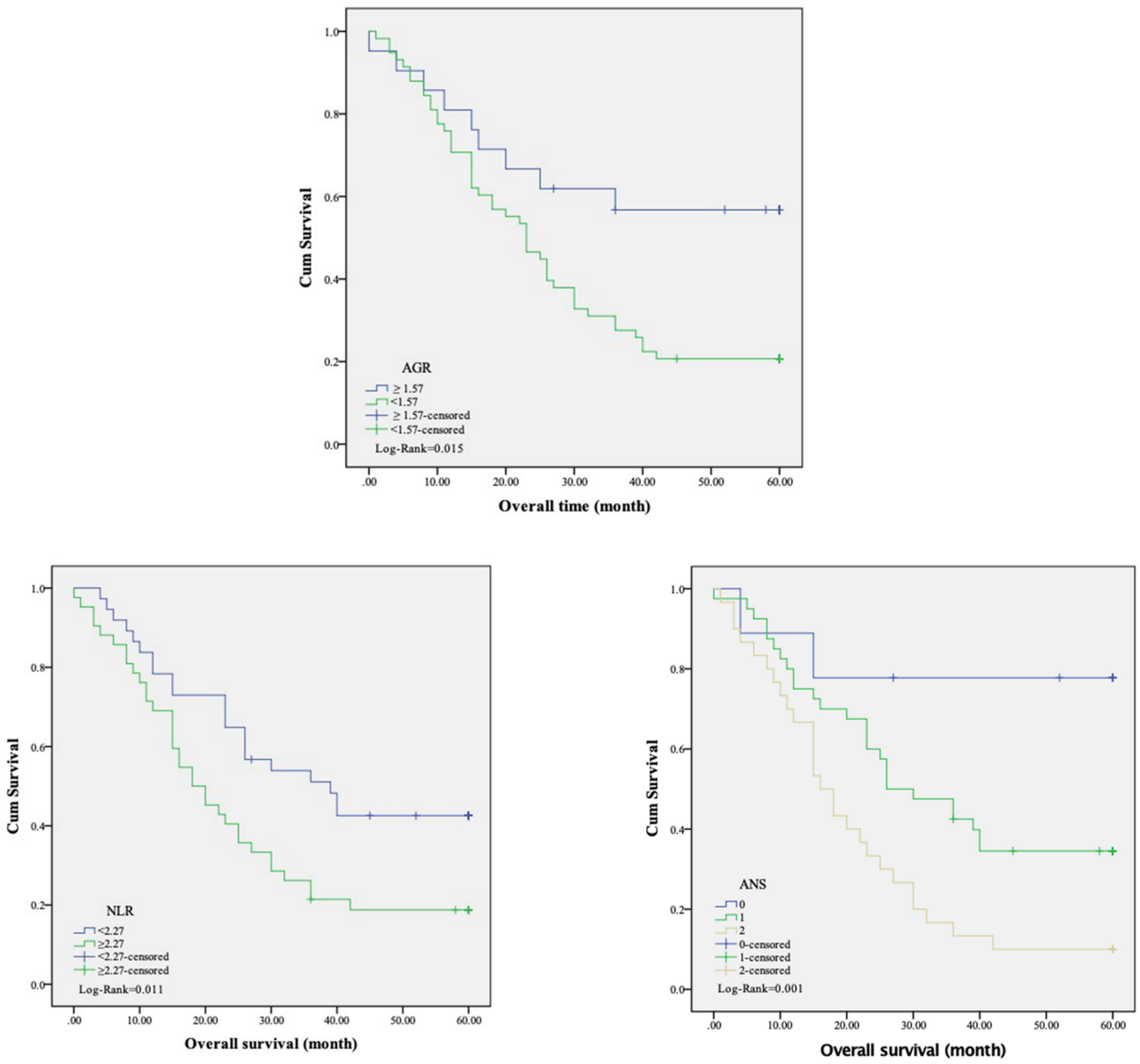

Figure 3 Kaplan-Meier plots show overall survival in patients with MM and RI, according to the AGR, NLR, and ANS scores.

New Prognostic Model for OS and PFS

Based on all the independent prognostic factors for OS and PFS identified with the Cox regression model, we created prognostic nomograms to facilitate predictions of survival for patients with MM and RI (Figure 5). The multivariate prognostic model for OS was based on the β2 microglobulin, eGFR, ECOG, and ANS, and it had a c-index of 0.785. The nomogram for PFS integrated the eGFR, ECOG, and ANS, and it had a c-index of 0.786. The performance of the nomograms were verified with calibration plots (Figure 6).

Discussion

The present study evaluated the prognostic performance of NLR, AGR, and ANS for predicting OS and PFS in patients with MM and RI. An elevated NLR and low AGR were strongly associated with a poor prognosis. In addition, the ANS was identified as an independent prognostic biomarker for both OS and PFS in patients with MM and RI. Finally, we

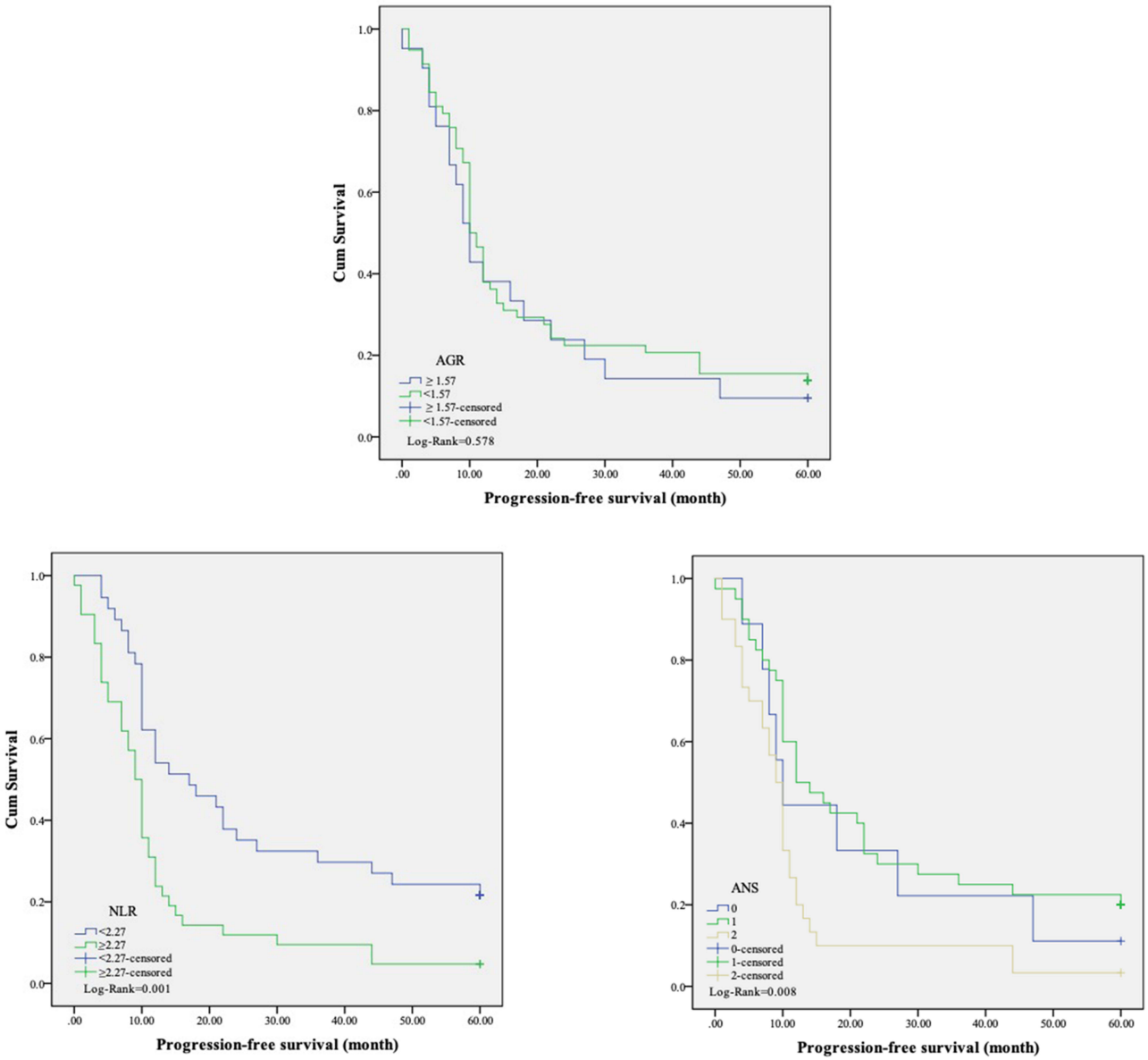

Figure 4 Kaplan-Meier plots show progression-free survival in patients with MM and RI, according to the AGR, NLR, and ANS scores.

established a novel nomogram that incorporated these biomarkers to improve the accuracy of predicting survival outcomes in patients with MM and RI.

Currently, it is widely known that some inflammatory cells include macrophages and lymphocytes, are involved in the coordination of MM microenvironment. Thus, systemic inflammatory markers (eg NLR and LMR) derived from white blood cells has attracted attention in MM patients.[19] In addition, a meta-analysis by Zhao, a higher NLR was significantly associated with poor prognosis in chronic kidney disease population.[20] Consistent with previous findings, our results showed that a high NLR was an independent indicator of short OS and PFS for patients with MM and RI. Several potential mechanisms might explain our findings. First, neutrophils are capable of secreting the pro-angiogenic molecule, vascular endothelial growth factor (VEGF). Studies have shown that circulating VEGF contributed to tumor angiogenesis and MM progression.[21] Furthermore, therapy that targeted VEGF improved the outcome in patients with MM.[22] In addition, studies have shown that neutrophils could suppress T-cell activation, including T-helper 17 cells and regulatory T cells; this activity led to a localized immunosuppressive microenvironment in MM, which had an adverse effect on patient survival.[23]

Table 5 Univariate and Multivariate Analysis of Prognostic Factors of Overall Survival and Progression-Free Survival by Cox Regression Model

Variable	Overall Survival				Progression-free Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age (>65)	1.13 (0.66–1.91)	0.661			0.95 (0.59–1.53)	0.844		
Gender (male)	1.51 (0.86–2.70)	0.152			1.35 (0.81–2.26)	0.254		
Hb (>90.0)	0.75 (0.42–1.31)	0.308			0.79 (0.47–1.33)	0.374		
RBC (>3.0)	1.11 (0.61–2.00)	0.740			1.13 (0.66–1.94)	0.653		
RDW (>15.3)	0.94 (0.51–1.73)	0.842			0.85 (0.49–1.45)	0.543		
WBC (>6.57)	1.80 (1.00–3.23)	0.049	1.14 (0.59–2.21)	0.691	1.51 (0.87–2.61)	0.143		
Platelet (>184.0)	0.86 (0.45–1.63)	0.858			1.15 (0.67–1.99)	0.614		
Urea (>14.5)	1.21 (0.66–2.21)	0.546			0.87 (0.49–1.54)	0.635		
Creatine (>447.2)	2.37 (1.30–4.32)	0.005	1.19 (0.58–2.42)	0.634	1.74 (0.97–3.14)	0.064		
ECOG (3–4)	3.12 (1.75–5.59)	0.000	2.77 (1.47–5.22)	0.002	2.20 (1.27–3.80)	0.005	2.35 (1.34–4.11)	0.003
eGFR (>50.5)	0.28 (0.13–0.59)	0.001	0.35 (0.16–0.77)	0.010	0.50 (0.29–0.88)	0.016	0.54 (0.30–0.94)	0.031
β2 microglobulin (>19.1)	2.49 (1.38–4.49)	0.002	2.58 (1.33–5.02)	0.005	1.29 (0.73–2.26)	0.377		
M protein type								
Ig G	1				1			
Ig A	0.49 (0.11–2.14)	0.342			0.63 (0.15–2.69)	0.534		
Light chain (L)	0.45 (0.97–2.06)	0.300			0.74 (0.17–3.29)	0.696		
Light chain (K)	0.39 (0.09–1.72)	0.215			0.56 (0.13–2.40)	0.435		
Ig D	0.32 (0.52–1.94)	0.213			0.40 (0.07–2.20)	0.291		
ISS Stage								
I	1				1			
II	0.64 (0.27–1.48)	0.295			0.85 (0.42–1.71)	0.649		
III	0.72 (0.31–1.65)	0.313			0.92 (0.40–1.82)	0.643		
Chemotherapy	1				1			
Stem cell transplant	0.87 (0.39–1.81)	0.769			0.39 (0.08–2.19)	0.517		
Renal response	0.79 (0.41–1.82)	0.422			0.49 (0.23–1.07)	0.071		
NLR (≥2.27)	1.98 (1.14–3.43)	0.015	1.82 (1.02–3.28)	0.044	2.19 (1.34–3.57)	0.002	2.34 (1.42–3.85)	0.001
AGR (≥1.57)	0.43 (0.21–0.88)	0.021	0.33 (0.16–0.68)	0.003	1.16 (0.68–1.96)	0.594		
ANS	2.27 (1.44–3.56)	0.000	2.25 (1.42–3.58)	0.001	1.57 (1.05–2.36)	0.029	1.54 (1.01–2.34)	0.044

Abbreviations: AGR, Albumin-globulin ratio; NLR, neutrophil-lymphocyte ratio; Hb, hemoglobin; RBC, red blood count; RDW, red cell distribution width; WBC, white blood count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; eGFR, estimated glomerular filtration rate; ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group performance status.

Albumin and globulin are two principal components of systemic inflammation. Previous studies in various populations have investigated how the combination of these two factors (ie, the AGR) was related to prognosis in many diseases, including myocardial infarction,[24] metastatic gastric cancer,[25] and clear cell renal cell carcinoma.[26] Furthermore, a low AGR was identified as a risk factor for cancer incidence and mortality in the general population.[27] In the present study, we found that the AGR was inversely correlated with all-cause mortality in patients with MM and RI. These results were supported by the following evidence. First, albumin binds to carcinogens and nitric oxide (NO). Moreover, albumin is necessary to stabilize cell growth.[28] In addition, hypoalbuminemia was found to be a strong risk factor for all-cause mortality, and this condition was prevalent among patients with MM.[29] The etiologies of hypoalbuminemia include malnourishment and protein loss, via the kidney. In addition, prior studies have found that albumin could mobilize polyunsaturated fatty acids from the liver, which led to the formation of anti-inflammatory molecules, including lipoxins, protectins, and resolvins.[30] Hence, hypoalbuminemia was associated with mortality, partially due to its proinflammatory effects. Second, globulin is commonly regarded as a marker of inflammation. It was produced by the immune organs and reflected inflammatory status, which marked by the immunoglobulins, acute reactive proteins and other serum proteins.[31] In our cohort, patients grouped into higher AGR group tended to have higher globulin level and lower albumin level, a trend

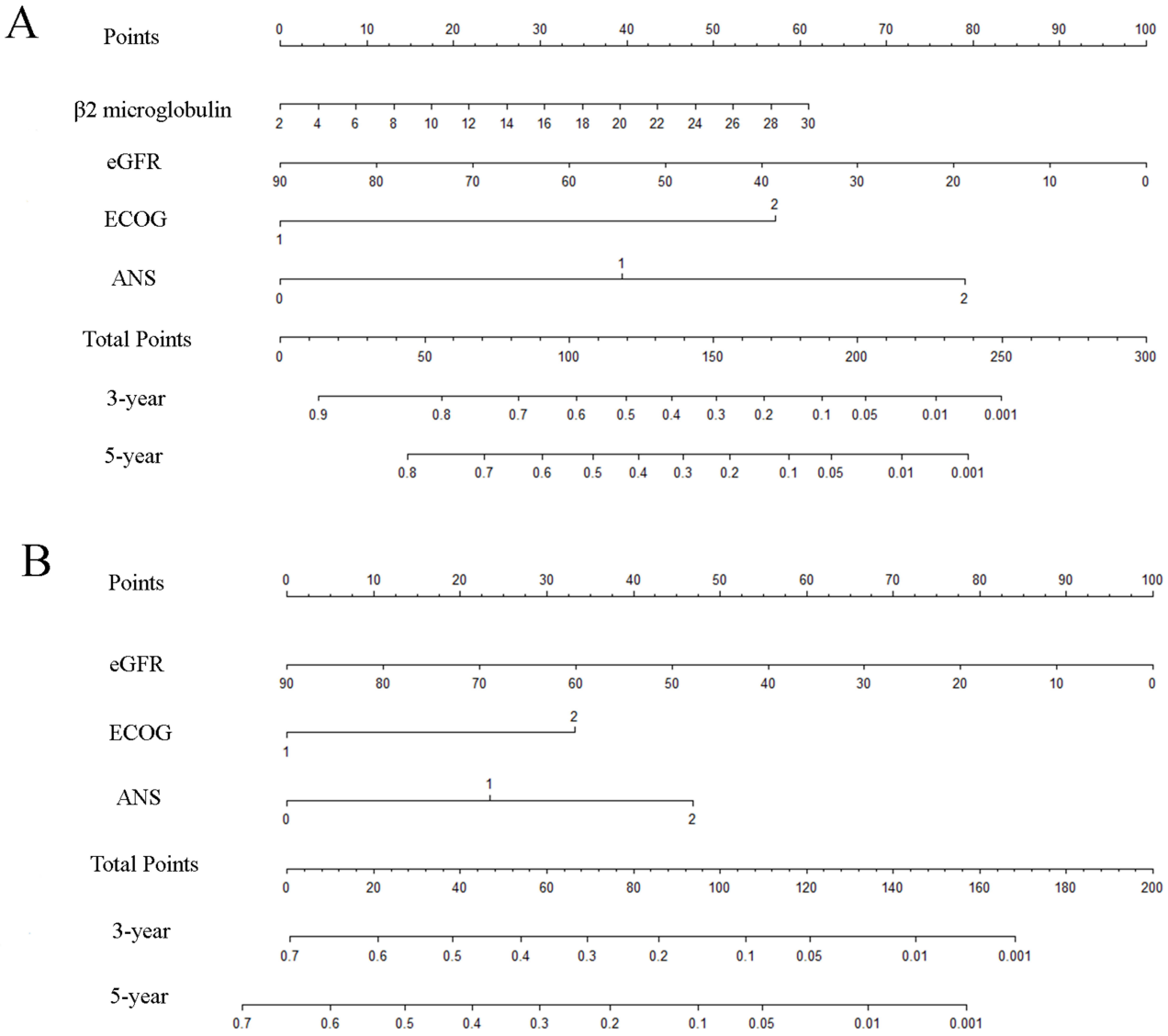

Figure 5 Nomograms for predicting the probability of survival in patients with MM and RI, based on the ANS and significant clinicopathologic characteristics. (**A**) Overall survival; (**B**) progression-free survival.

which is characterized for various inflammatory status, such as chronic inflammation or chronic active inflammation and late phase of acute inflammation. Therefore, a lower AGR maybe driven by low serum albumin concentration, high globulin level of a combination of both, and in this way the biomarker combined two prognostic predictors of survival that is independent of fluid status. This condition was predominantly related to poor prognosis in malignant tumors but also in chronic kidney disease patients.[32,33] Consequently, the predictive value of AGR may be enhanced for the population of patients with MM and RI.

Our study has extended knowledge from previous studies by identifying the ANS as a prognostic factor for OS and PFS in patients with MM and RI. Elevated NLR and reduced AGR have been identified as risk factors for all-cause mortality, and the combination of these two markers, in the ANS, was found to predict the risk of mortality better than either individual measure alone in patients with breast cancer.[34] To the best of our knowledge, this study was the first to demonstrate that the ANS could serve as a potential prognostic biomarker for OS and PFS in patients with MM and RI. Our results revealed that a higher ANS was an independent factor and has improved predictive power compared with AGR and NLR for predicting the prognosis for 5-year OS and PFS in patients with MM and RI.

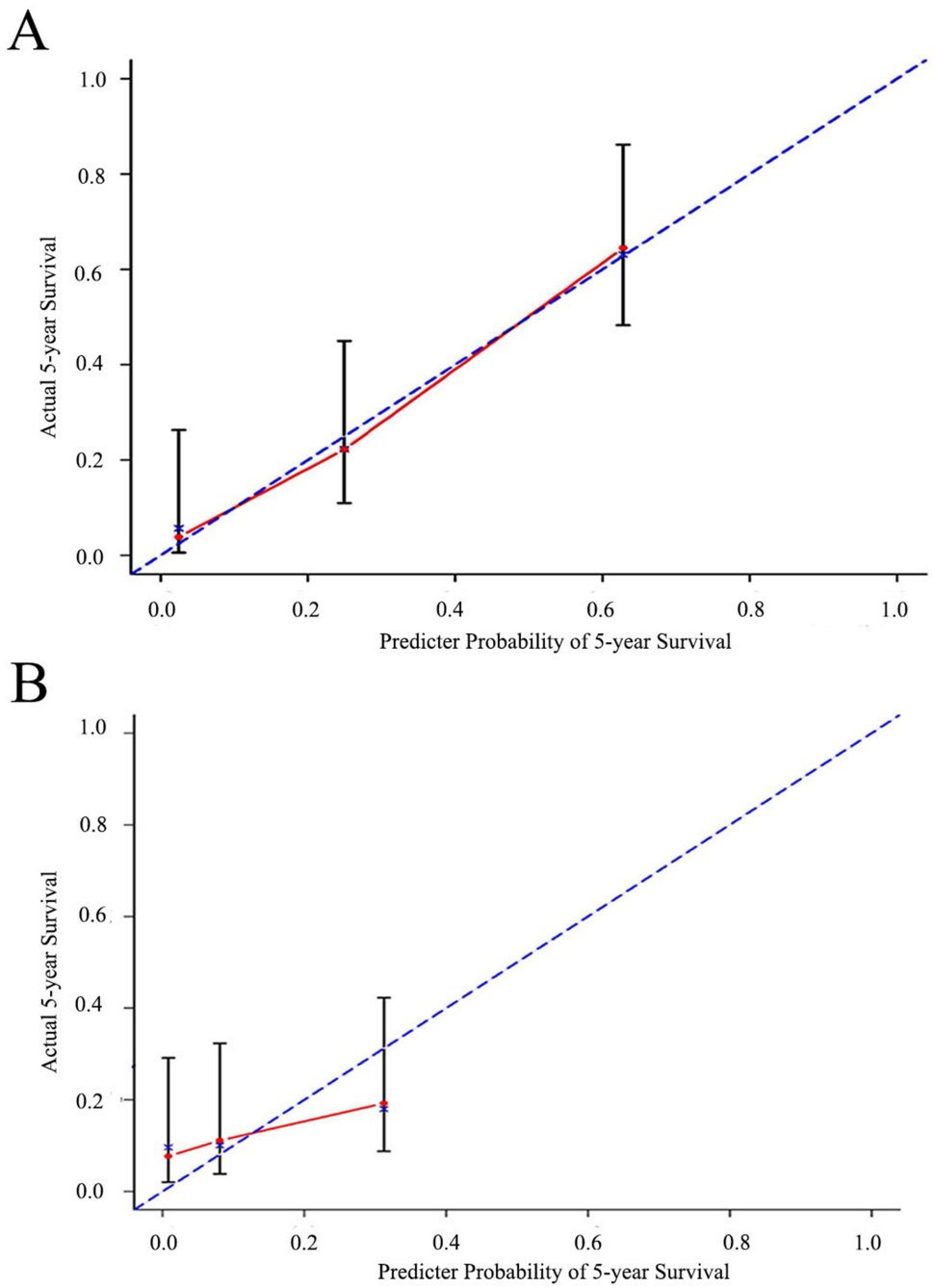

Figure 6 Calibration plots validate the nomograms for predicting survival of patients with MM and RI. (**A**) 5-year overall survival; (**B**) 5-year progression-free survival.
Notes: The 45-degree reference line represents the performance of a perfect nomogram. The red dashed line shows the performance of the observed nomogram. It seems that the nomogram precisely predicts the 5-year OS and PFS. n = 79; d = 55; P = 4; 20 subjects per group, n = 79 for OS; d = 69; P = 3; 20 subjects per group for PFS; X-resampling optimism added, B = 200; comparison between nomogram-predicted probability of OS and PFS (X-axis) and the actual 5-year survival (Y-axis).

Several nomograms were previously developed for predicting OS in various diseases, based on clinical characteristics.[35] Indeed, nomograms can be considered an excellent alternative to traditional staging systems for predicting prognosis in cancers.[36] The present study developed nomograms for predicting 5-year mortality and recurrence in patients with MM and RI. These nomograms included the ANS and several clinical pathological factors. Our nomograms performed well for predicting OS and PFS, and the results were supported by the c-index (0.785 and 0.786, respectively). These findings suggested that the derived nomograms might improve predictions of prognosis in patients with MM and RI.

This study had several limitations. First, the study design was retrospective, it was conducted in a single center, and our cohort was relatively small. These limitations might have introduced biases in the data collection and analyses. Second, other biomarkers of inflammation, such as the platelet-to-lymphocyte ratio and the lymphocyte-to-monocyte ratio were not measured in our cohort. Third, we only analyzed the baseline of biomarkers in our analysis, without considering the impact of variations during the follow-up period. Future studies are needed to investigate in more detail the relationship between inflammatory biomarkers and prognosis in patients with MM and RI.

Conclusions

This study demonstrated that the NLR, AGR, and ANS were significantly associated with prognosis in patients with MM and RI. Moreover, the NLR and ANS were independent predictors of both OS and PFS, and the AGR was an independent prognostic predictor for OS in patients with MM and RI. Therefore, the integration of the NLR and AGR in the ANS and the newly developed predictive nomograms may be valuable tools for evaluating prognosis and for determining optimal therapeutic strategies for patients with MM and RI.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors declare no competing interests in this work.

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