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ORIGINAL RESEARCH

A Nomogram Based on Circulating Inflammatory Factors for Predicting Prognosis of Newly Diagnosed Multiple Myeloma Patients

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Purpose: The growth and survival of multiple myeloma (MM) cells depend heavily on bone marrow microenvironment, where inflammation emerges as a significant feature and is commonly associated with unfavorable prognosis in MM. Our previous study and other published studies have shown that MM patients with higher neutrophil-to-lymphocyte ratio (NLR) or interleukin (IL)-10 (IL-10), lower lymphocyte-to-monocyte ratio (LMR) or platelet-to-lymphocyte ratio (PLR) frequently have inferior overall survival (OS) independent of current risk- stratification markers. Nevertheless, whether specific inflammation-related markers have prognostic value for MM patients remains elusive.

Patients and methods: We retrospectively analyzed the clinical data of 452 newly diagnosed MM (NDMM) patients treated in our center from May 2013 to June 2022. Cox regression analysis and least absolute shrinkage and selector operation (LASSO) were performed to establish the predictive nomograms for survival outcomes in the training cohort, and the nomograms were validated by calibration curves in the validation cohort.

Results: The best cutoff values of NLR, LMR, PLR, and IL-10 were 4.44, 4.0, 100, and 1.42pg/mL, respectively. We established a nomogram model after LASSO Cox and multivariate Cox regression analysis. The nomogram model exhibited acceptable discrimination, with C-index values of 0.777, 0.714, and 0.71 in the training cohort, validation cohort, and entire cohort, respectively, which was significantly higher than the C-indices of the three most extensively used staging systems for NDMM (D-S, ISS, and R-ISS). All calibration curves revealed good consistency between the predictive and actual survival outcomes. Patients were divided into high-risk and low-risk groups based on their total nomogram scores, with a threshold of 106.2, where the median OS of patients in the high-risk group was significantly shorter than that of patients in the low-risk group.

Conclusion: The proposed nomogram based on circulating inflammatory factors is an inexpensive, widely available, and easily interpretable risk-stratification tool for NDMM patients.

Keywords: multiple myeloma, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, lymphocyte to monocyte ratio, IL-10, nomogram

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy in adults and is characterized by clonal proliferation of plasma cells in bone marrow, leading to hypercalcemia, anemia, renal insufficiency, and bone destruction.[1,2] Within the last decade, the prognosis of MM patients has been significantly improved with the clinical application of various novel targeted drugs such as proteasome inhibitors, immunomodulatory drugs,

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and monoclonal antibodies. More and more MM patients also underwent autologous hematopoietic stem cell transplantation (ASCT) to achieve superior survival.[3–5] However, MM remains an incurable disease, with the vast majority of patients ultimately experiencing relapse and refractory disease.[6,7]

MM is a disease marked by significant biological diversity and variation of clinical characteristics, resulting in heterogeneity of survival outcomes in patients with newly diagnosed multiple myeloma (NDMM), even those who receive novel therapies. Therefore, risk-adapted treatment strategies based on optimal risk stratification are of great importance for NDMM patients.[8,9] The ISS is widely used for risk assessment in MM patients based on serum β2-microglobulin and albumin levels, which correlate with tumor burden and patient fitness, respectively. While simple and easily applicable, the ISS does not account for other prognostic factors such as cytogenetic abnormalities or molecular markers, which can significantly influence treatment response and survival.[10] The R-ISS incorporates additional parameters, including lactate dehydrogenase (LDH) levels and high-risk cytogenetic features (eg, t(4;14), t(14;16), del17p), into the original ISS framework.[11] Despite its improved prognostic accuracy compared to ISS, the R-ISS still faces challenges related to the accessibility and standardization of biomarker testing across different healthcare settings. Overall, a more readily available and inexpensive prognostic stratification system remains meaningful for NDMM patients.

It is widely recognized that the tumor microenvironment plays a pivotal role in the progression of MM. MM cells depend on signals generated by various cells within their microenvironment to support their survival and proliferation.[1] The tumor microenvironment harbors multiple inflammatory cells and cytokines, which could promote tumor transformation and progression through diverse mechanisms, and are frequently associated with inferior prognosis across various types of cancers.[12] With the deepening of the understanding of the tumor inflammatory microenvironment, we found that inflammation plays an important role in the occurrence, growth, and development of tumors.[13] Research has shown that inflammatory cells and cytokines in the blood can reflect the state of immune inflammation within a patient's body, significantly influencing the tumor microenvironment and the progression of malignant diseases, and are associated with the prognosis of cancer patients.[13–16] Inflammatory cells in the blood and systemic inflammatory response have a considerable impact on the tumor microenvironment and the progression of malignant diseases and are related to the prognosis of tumor patients.[13] Previous studies have demonstrated that multiple inflammation-related factors based on peripheral blood cell counts, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), as well as cytokines such as interleukin (IL)-6, IL-10, and IL-17A, have significantly predictive value for outcomes in different kinds of tumors including MM, colorectal cancer, non-small cell lung cancer, and breast cancer.[12,17–20] Several studies have shown that elevated NLR and IL-10, decreased LMR and PLR are significantly associated with adverse clinical features and poor prognosis in MM.[12,17–19,21–23] However, while individual markers were studied, no integrated model was developed using readily available markers. Up to date, there is lacking an integrated stratification system based on circulating inflammatory factors for NDMM patients.

In this study, we explored the potential of inflammatory markers obtained from peripheral blood as predictive indicators for the survival outcomes of patients with NDMM. Our objective was to establish and validate a comprehensive prognostic model that integrates various inflammatory biomarkers, thereby enhancing risk stratification for NDMM patients in the context of contemporary therapeutic approaches.

Methods

Patients and Treatments

This study was a retrospective analysis approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine, with a total of 452 NDMM patients with complete clinical data enrolled between May 2013 and June 2022. The samples used in this study were collected as part of other ongoing or completed studies. All NDMM patients received the first-line treatment with a bortezomib-based regimen in our center, including either a PD regimen (bortezomib combined with dexamethasone), PCD regimen (bortezomib, dexamethasone combined with cyclophosphamide), PAD regimen (bortezomib, dexamethasone combined with adriamycin), or PTD regimen

(bortezomib, dexamethasone combined with thalidomide). The specific administration method has been reported in detail.[24] Treatment efficacy was evaluated after each cycle according to the IMWG efficacy criteria.

Data Acquisition

All patients were hospitalized during the initial diagnosis and each course of treatment. At the time of diagnosis, prognosis assessment was performed with Durie-Salmon (D-S) staging, the international staging system (ISS), and revised-ISS staging (R-ISS). Data regarding routine blood examinations, hepatic and renal function indicators, lactate dehydrogenase (LDH) level, C-reactive protein (CRP), and results of bone marrow aspiration were obtained from the hospital Patients Records System (PRS). NLR, LMR, PLR, SII, and SIRI were obtained from peripheral blood and defined as follows: NLR=absolute neutrophil count/ absolute lymphocyte count, LMR= absolute lymphocyte count/ absolute monocyte count, PLR=absolute platelet count/ absolute lymphocyte count, SII=absolute platelet count× NLR, and SIRI=absolute neutrophil count× the ratio of monocyte count/lymphocyte count.

The serum concentrations of circulating cytokines, including IL-2, IL-4, IL-6, IL-10, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-17A were quantified using a cytometric bead array (CBA) kit, namely the BD™ CBA Human Th1/Th2/TH17 Cytokine Kit (BD Biosciences, San Jose, CA, USA). The minimum and maximum detection limits for all 7 cytokines were 0.10 pg/mL and 5000 pg/mL, respectively. Cytokine measurement was performed according to the manufacturer's protocol. The samples used in this study were collected as part of other completed studies. In brief, 3–5 mL patient's peripheral blood samples were collected and centrifugated to obtain the serum. Serum samples were stored at 2–8°C, and were tested within 24 hours. Add the serum samples into the capture microsphere mixture containing 7 kinds of cytokine-specific antibodies (25uL/tube). After thorough mixing by vortex, the mixture was incubated in the dark for 30 minutes to allow specific binding between the serum samples and the antibodies on the microsphere surface. Subsequently, PE-labeled fluorescent detection reagent (25 μL) was added to each tube. After thorough mixing by vortex, the mixture was incubated in the dark for 90 minutes to make the capture microsphere, samples, and detection antibody to form a double-antibody sandwich complex. Each group of samples was set up with three replicates. The fluorescence intensity of the double-antibody sandwich complex was then analyzed using a BD FACScanto™ II flow cytometer (Becton Dickinson, San Jose, CA, USA). Data were generated in both graphical and tabular formats using FCAP Array™ software (BD Biosciences, San Jose, CA, USA) to determine the concentrations of cytokines in the samples. From the beginning of treatment to the end of the follow-up of this study, all patients could stay informed of their condition and survival through inpatient data, as well as outpatient or telephone follow-up.

We adopted a comprehensive approach based on the extent and nature of the missing data. For datasets with numerous missing values, we implemented a comprehensive deletion to eliminate all such entries. This approach was chosen to minimize potential biases that could arise from imputation in cases where the proportion of missing data was high. Conversely, for datasets where missing data was less prevalent, we employed an imputation strategy. The missing entries were substituted with the mean of all available, non-missing values within the respective variable. This method was selected to maintain the integrity of the dataset while ensuring statistical rigor.

Construction and Validation of a Predictive Nomogram Model for Outcomes

Using a random number list generated by SPSS, the 452 NDMM patients were randomly divided into a training cohort of 320 patients and a validation cohort of 132 patients with a ratio of 7:3. The 7:3 split between training and validation cohorts was chosen to balance the needs of model training and validation under limited data conditions, ensure that the model has good generalization ability, and effectively avoid overfitting problems. The training cohort was used to establish the OS nomograms. Univariate analysis of potential risk factors for OS was performed using the Cox proportional hazards regression model. Least absolute shrinkage and selection operator (LASSO) Cox regression analysis, a simple, effective, interpretable, and less overfitting methodology, was used for the selection of variables into the nomogram. A 5-fold cross-validation procedure was performed using LASSO Cox regression. Significant variables with $P<0.1$ in univariate analysis were included in the multivariate Cox regression and LASSO Cox regression analyses. Parameters with nonzero coefficients were incorporated into the nomogram system based on circulating inflammatory factors.

The prognostic performance of the nomogram was validated by measuring the values of discrimination and calibration in the training cohort, validation cohort, and entire cohort. The predictive power of the nomogram was assessed by the C-index (concordance index), with a higher C-index indicating a better ability to discriminate outcome variability for patients. A calibration curve from 1000 bootstrap replicates was used to assess the conformity between the model-predicted probability and actual conditions. The predictive ability of the nomogram was evaluated using time-dependent receiver operating characteristic (ROC) curves and area under the curve (AUC) in the training cohort, validation cohort, and entire cohort. The net benefit of the novel nomogram was measured with decision-curve analysis (DCA). Patients were classified into high- and low-risk groups based on the nomogram risk scores.

Statistical Analysis

Statistical analyses were conducted using SPSS 26.0 software (SPSS, Chicago, IL, USA) and R software (Version 4.3.3, R Project for Statistical Computing, Vienna, Austria). ROC curve analysis was performed to determine the optimal cut-off values of continuous variables based on the maximum Youden index. Non-normally distributed data were expressed as medians and compared using the Mann–Whitney *U*-test; count data were expressed as percentages and compared using the chi-square test or Fisher's exact test. Overall survival (OS) was measured from *de novo* diagnosis to death or the final follow-up visit. The Kaplan-Meier method was used to generate survival curves, and the differences between survival curves were compared using Log rank tests. Logistic regression analysis and a Cox proportional hazards model were used to perform univariate and multivariate analyses, which were displayed as hazard ratios (HRs), and 95% confidence intervals (CIs). All test results were bilateral. A p-value < 0.05 indicated statistical significance, and factors with p-value < 0.1 were entered into multivariate analysis. The rms package in R was used to plot the nomogram and formulate a calibration curve. The DCA curve was plotted in R using the stdca package. Statistical significance was defined as a two-tailed *P*-value of < 0.05.

Results

Clinical Characteristics

The clinical and laboratory characteristics of patients at diagnosis in the training and validation cohorts are summarised in Table 1. A total of 452 NDMM patients were enrolled, with a median age of 62.3±9.3 years (range: 31–84); 252 (56.0%) patients were male and 199 (44.0%) were female. There were no significant differences between patients in the training and validation groups according to sex, type of M protein; D-S, ISS, or R-ISS stage; levels of hemoglobin (Hb), platelets (Plt), albumin, creatinine (Cr), C-reactive protein (CRP), or ferritin, the existence of extramedullary myeloma at diagnosis, cytogenetic abnormalities, or osteolytic lesions, or treatment efficacy after four courses, first-line therapy regimens, or undergoing ASCT.

The Relationship Between Circulating Inflammatory Factors, Clinical Characteristics, and Survival Outcomes

The optimal cutoff value of the circulating inflammatory factors was based on the receiver operating characteristic (ROC) curve in the training cohort. The median time of follow-up was 41.9 months (range:0.97–95), 42.3 months (range:0.97–95.0), and 38.7 months (range: 2.2–89.5) in the entire cohort, training cohort, and validation cohort, respectively (P=0.087). The median OS was 71.4 months (range: 0.97–95.0) for all patients in the entire cohort with the median OS of 68.4 months (range: 0.97–95.0) in the training cohort and 68.0 months (range: 2.2–89.5) in the validation cohort (P=0.448). The Kaplan–Meier survival curves according to the circulating inflammatory factors in the training cohort are shown in Figure 1. Compared to patients in the NLR ≥ 4.44 group, patients in the NLR<4.44 group had poorer OS (38.2 months vs 71.4 months, P=0.011). Compared to patients in the LMR>4 groups, patients in the LMR≤4 group had worse OS (59.6 months vs NR, P=0.031). Patients with PLR>100 had superior OS to patients with PLR≤100 (85.7 months vs 50.6 months, P=0.001). Patients with SII <1574 had superior OS to patients with SII ≥1574 (71.4 months vs 38.1 months, P=0.028). The OS of patients with ferritin<223ug/L was superior to that of patients with ferritin ≥223ug/L (NR vs 54.7 months, P<0.001). The OS of patients with IL-10<1.42pg/mL was superior to that of patients with IL-10

Table 1 Baseline Characteristics for Newly Diagnosed Multiple Myeloma Patients

	Training Cohort, N=320 (%)	Validation Cohort, N =132(%)	P value
Age			0.005
≤68 years	245(63.6)	84(76.6)	
>68years	75(36.4)	48(23.4)	
Gender			0.854
Male	180(55.3)	73(56.3)	
Female	140(44.7)	59(43.8)	
Type of M protein, n (%)			0.780
Non-IgD	303(94.7)	124(95.3)	
IgD	15(5.3)	7(4.7)	
D-S stage, n (%)			0.144
1+2	65(28.8)	38(20.3)	
3A	203(57.6)	76(63.4)	
3B	52(13.6)	18(16.3)	
ISS stage, n (%)			0.616
1	92(32.6)	43(28.8)	
2	97(31.1)	41(30.3)	
3	131(36.4)	48(30.7)	
R-ISS stage, n (%)			0.097
1	30(14.8)	18(11.5)	
2	129(57.4)	70(49.4)	
3	102(27.9)	34(29.1)	
Unknown	10	59	
Hb (g/L), median (IQR)	94.0(76.0–1113.8)	94.5(79.3–117.8)	0.705
≥100	134(41.9)	54(40.9)	0.850
<100	186(58.1)	78(50.1)	
Plt ($\times 10^9$/L), median (IQR)	190.8(116.0–227.0)	180.9(136.5–239.0)	0.158
≥150	201(62.8)	85(64.4)	0.751
<150	119(27.2)	47(35.2)	
CRP (g/L), median (IQR)	10.3(0.7–8.1)	8.7(0.6–5.9)	0.995
≤8	232 (75.6)	102(80.3)	0.286
>8	75(24.4)	25(19.7)	
LDH (u/L), median (IQR)	256.6(153.0–237.0)	213.2(135.8–211.0)	0.006
<245	244(77.7)	108(83.1)	0.204
≥245	70(22.3)	20(16.9)	
Cr(umol/L), median (IQR)	132.4()	137.8()	0.874
≤177	264(82.5)	111(84.7)	0. 565
>177	56(17.5)	20(15.3)	
Albumin(g/L), median (IQR)	38.8(32.8–43.4)	37.8(33.6–43.9)	0.335
≤30	274(85.6)	109(83.2)	0.515
>30	46(14.4)	22(16.8)	
Ferritin(g/L), median (IQR)	554.9(190.6–624.1)	554.7(142.5–493.4)	0.058
≤223	90(31.3)	37(32.2)	0.857
>223	198(68.8)	78(67.8)	
BMPCs (%), median (IQR)	26.7(12.5–47.0)	32.2(13.4–35.3)	0.030
≤30	165(51.6)	84(64.1)	0.015
>30	155(48.4)	47(35.9)	
Osteolytic lesions			0.604
≤2 lesions	255(79.7)	108(81.8)	
>2 lesions	65(20.3)	24(18.2)	

(*Continued*)

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Table 1 (Continued).

	Training Cohort, N=320 (%)	Validation Cohort, N =132(%)	P value
EMM at diagnosed			0.060
Non-EMM	238(74.4)	109(82.6)	
EMM	82(25.6)	23(17.4)	0.998
EMB	69(84.1)	20(87.0)	
EME	13(15.9)	3(13.0)	
Treatment efficacy			0.941
≥PR	294(91.9)	121(91.7)	
<PR	26(8.1)	11(8.3)	
Therapy received			0.782
PD	67(21.9)	25(20.5)	
PAD	36(10.1)	9(7.4)	
PCD	166(54.2)	69(56.6)	
PTD or PRD	42(13.7)	19(15.6)	
FISH			
1q gain/amp	91(36.5)	41(34.7)	0.737
Del 17p	12(4.8)	4(3.4)	0.531
Del 13q	56(25.7)	23(24.0)	0.745
14 qrearrangement	68(28.2)	17(15.2)	0.008
Unknown	71	14	
ASCT			0.661
No	278(87.1)	113(85.6)	
Yes	41(14.9)	19(14.4)	

Abbreviations: D-S, Durie-Salmon; ISS, international staging systems; R-ISS, revised-ISS; Hb, hemoglobin; Plt, platelets; CRP, C-reactive protein; LDH, lactate dehydrogenase; Cr, creatinine; BMPCs, bone marrow plasma cells; EMM, extramedullary multiple myeloma; EMB, extramedullary bone-related lesions; EME, extramedullary extraosseous lesions; PR, partial remission; FISH, fluorescence in situ hybridization; ASCT, autologous hematopoietic stem cell transplantation.

≥1.42pg/mL (P<0.001). There was no significant impact of circulating inflammatory factors, including CRP, IL-2, IL-4, IL-6, TNF-a, IFN-γ, and IL-17a, on the OS of NDMM patients.

We further analyzed the relationship between the abovementioned circulating inflammatory factors and the clinical characteristics of NDMM patients (Supplementary Table 1). The results showed that patients with NLR≥4.44, LMR≤4, PLR≤100, ferritin ≥223ug/L, or IL-10≥1.42pg/mL had a greater tendency of being stratified into high-risk D-S and ISS stages (P<0.05). In addition, patients with NLR≥4.44, LMR≤4, or IL-10≥1.42pg/mL were more likely to have elevated serum LDH and Cr levels at diagnosis (P<0.05).

Nomogram Model for a Risk-Stratification System Based on Circulating Inflammatory Factors

To construct a nomogram based on circulating inflammatory factors, we selected 14 indicators, including NLR, LMR, PLR, SII, SIRI, CRP, ferritin, IL-2, IL-4, IL-6, IL-10, TNF-a, IFN-γ, and IL-17a for further analysis. In the training cohort, univariate Cox regression analyses showed that a total of 10 variables, including NLR, LMR, PLR, SII, SIRI, CRP, ferritin, IL-2, IL-10, and IFN-γ were considered as potential predictors for OS (P<0.1) (Table 2). To avoid overfitting, LASSO regression was performed using those ten variables in the training cohort. Six variables, including NLR, LMR, PLR, SIRI, ferritin, and IL-10, with nonzero coefficients were retained in the LASSO analysis (Figure 2A and B).

The variables that showed significance in the univariate and LASSO regression analyses were included in the multivariate Cox proportional hazards analysis. Therefore, we used these six retained variables for further multivariate analysis, in which NLR (≥4.44 vs <4.44, HR=2.85, P=0.026), LMR (≤4.00 vs >4.00, HR=2.09, P=0.042), PLR (≤100 vs >100, HR=4.01, P<0.001), and IL-10 (≥1.42pg/mL vs <1.42pg/mL, HR=2.05, P=0.037) were validated as independent

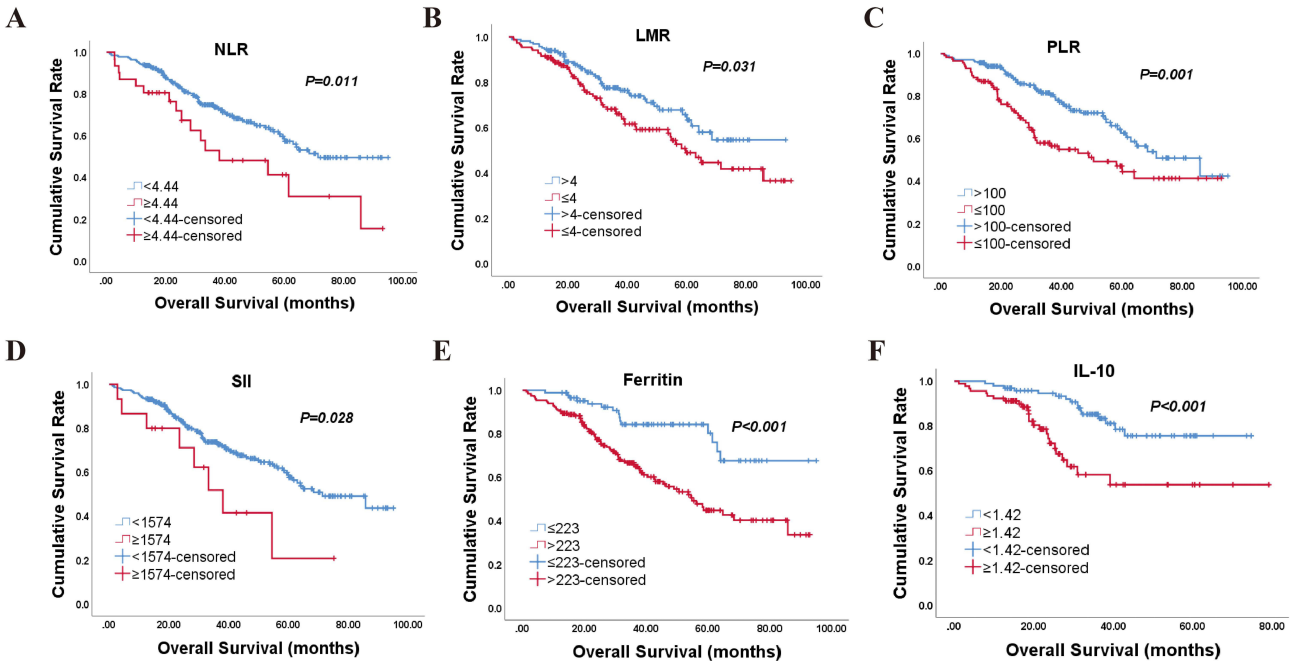

Figure 1 Relationship between circulating inflammatory factors and survival of NDMM patients. (**A-F**) Overall survival (OS) of NDMM patients in the training cohort based on serum NLR(**A**), LMR(**B**), PLR(**C**), SII(**D**), ferritin (**E**), and IL-10 (**F**) levels.

predictors for OS of NDMM patients (Table 2). Thus, these four independent predictors of OS were selected to establish the nomogram to predict the 1-, 3- and 5-year survival rates (Figure 2C). The C-index of the nomogram for discriminating for OS in the training cohort was 0.777 (95% CI: 0.712–0.842), and the calibration plots showed a good agreement between the predicted OS and actually observed OS (Figure 3A). In the validation cohort and entire cohort, the C-index of the nomogram was 0.714 (95% CI: 0.571–0.857) and 0.710 (95% CI: 0.696–0.830), respectively (Table 3). The calibration plots also showed good agreements between the predicted OS and actually observed OS in both the validation cohort (Figure 3B) and the entire cohort (Figure 3C). However, the C-indices of the D-S staging system were 0.594 (95% CI: 0.514–0.674), 0.562 (95% CI: 0.458–0.666), and 0.585 (95% CI: 0.520–0.649) in the training cohort, validation cohort, and entire cohort, respectively (Table 3). Similarly, the C-indices of the ISS staging were 0.570 (95% CI: 0.482–0.658), 0.681 (95% CI: 0.551–0.810), and 0.606 (95% CI: 0.533–0.679); and the C-indices of the R-ISS staging system were 0.589 (95% CI: 0.501–0.677), 0.679 (95% CI: 0.541–0.811), and 0.615 (95% CI: 0.542–0.688) in the training cohort, validation cohort, and entire cohort, respectively (Table 3). Therefore, the C-index of our novel nomogram based on circulating inflammatory factors was much higher than those of the currently widely used D-S, ISS, and R-ISS staging systems, which suggests that our novel nomogram is a more accurate and valuable tool for the prediction of OS in NDMM patients. Superior results were also observed for the ROC curves and the AUC of our novel nomogram compared with those of the D-S, ISS, and R-ISS staging systems (Figure 3D-F). The 2-year DCA further demonstrated that our novel predictive model based on circulating inflammatory factors exhibited a better net benefit within a range of tolerable threshold probabilities in the training, validation, and entire cohorts (Figure 4A-C).

Optimal Distinguishing of High-Risk and Low-Risk Patients Based on Total Nomogram Score

According to NDMM patients in this study, we found that the D-S stage could not accurately distinguish the prognosis of NDMM patients in stages I, II, and III in the entire cohort (Figure 5A). The ISS stage could not distinguish the prognosis of patients between stage I and II in the entire cohort (Figure 5B). While the R-ISS stage showed a good prognostic stratification for patients in stages I, II, and III in the entire cohort (Figure 5C). Each patient was given a total score for OS based on our nomogram model. Based on the OS threshold of 106.2, patients were divided into high-risk groups and

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Table 2 Univariable and Multivariable Analysis for OS

Variable	Univariable Analysis		Variable	Multivariable Analysis	
	HR (95% CI)	P value		HR (95% CI)	P value
Age ≥ 68 years	2.08(1.47–2.95)	<0.001	NLR ≥4.44	2.79(1.12–6.98)	0.028
Gender Male	0.76(0.54–1.07)	0.122	LMR ≤4.00	1.98(1.01–3.89)	0.046
Type of M protein IgD	2.01(1.11–3.64)	0.021	PLR ≤100	4.45(2.25–8.78)	<0.001
D-S 3B vs 1–3A	2.39(1.61–2.56)	<0.001	IL-10 ≥1.42pg/mL	2.24(1.16–4.34)	0.016
ISS 3 vs 1–2	1.95(1.39–2.73)	<0.001			
R-ISS 3 vs 1–2	2.52(1.72–3.69)	<0.001			
Hgb <100g/L	1.70(1.18–2.44)	0.004			
Plt ≥150×10^9/L	1.98(1.41–2.76)	<0.001			
LDH ≥245 u/L	2.56(1.80–3.69)	<0.001			
Cr ≥177 umol/L	1.98(1.33–2.96)	0.001			
Albumin <30 g/L	0.43(0.19–0.98)	0.044			
BMPCs ≥ 30%	1.91(1.36–2.68)	<0.001			
NLR ≥4.44	1.85(1.14–3.01)	0.013			
LMR ≤4.00	0.60(0.43–0.84)	0.003			
PLR ≤100	0.49(0.35–0.68)	<0.001			
SII ≥1574	2.51(1.32–4.79)	0.005			
SIRI ≥1.04	1.63(1.15–2.29)	0.006			
CRP ≥8mg/L	1.64(1.15–2.35)	0.007			
Ferritin >223ug/L	2.74(1.70–4.42)	<0.001			
IL-2 ≥0.16pg/mL	1.66(0.99–2.78)	0.054			
IL-4 ≥1.86pg/mL	0.55(0.17–1.76)	0.310			
IL-6 ≥0.48pg/mL	0.79(0.40–1.57)	0.505			
IL-10 ≥1.42pg/mL	3.87(2.34–6.71)	<0.001			
TNF-α ≥0.17pg/mL	1.56(0.91–2.68)	0.105			
INF-γ ≥0.54pg/mL	1.66(0.96–2.88)	0.071			
IL-17A ≥1.29pg/mL	1.50(0.84–2.70)	0.172			

Abbreviations: OS, overall survival; HRs, hazard ratios Cis, confidence intervals; D-S, Durie-Salmon; ISS, international staging systems; R-ISS, revised-ISS; Hb, hemoglobin; Plt, platelets; CRP, C-reactive protein; LDH, lactate dehydrogenase; Cr, creatinine; BMPCs, bone marrow plasma cells; NLR neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, system Inflammation Response Index; IL-2, interleukin-2; TNF-α, tumor necrosis factorα; IFN-γ, interferon-γ.

low-risk groups by nomogram scoring in the training, validation, and entire cohorts, respectively. Survival analysis showed that patients with high-risk had significantly inferior OS compared to patients with low-risk either in the training, validation, or entire cohorts (P<0.001), where the median OS was 28.5 months vs NR (95% CI: 22.4–34.5), 52.4 months vs NR, and 29.4 months vs NR (95% CI: 23.8–34.9) in the three cohorts, respectively (Figure 5D-F). Therefore, our nomogram scoring system based on circulating levels of four inflammatory factors at diagnosis, including NLR, LMR, PLR, and IL-10, showed excellent power to predict OS for NDMM patients.

Discussion

Systemic inflammatory markers derived from peripheral blood-cell counts (NLR, PLR, and LMR) have recently received a great deal of attention in MM. Several studies have shown that elevated NLR and decreased LMR and PLR are significantly associated with adverse clinical features and poor prognosis in MM.[12,17,18,21] Despite the significant role of inflammatory factors in the prognosis of MM patients, they have not been adequately recognized to use as risk estimation in clinical treatment. Lymphocytes play a significant role in immune surveillance, and an increased number of infiltrating lymphocytes in the tumor microenvironment may serve as a favorable prognostic indicator.[25] The absolute count of neutrophils in peripheral blood serves as a critical indicator of systemic inflammation, which fosters an environment conducive to the onset and progression of malignant tumors.[26] Hence, NLR can serve as an indicator that partially

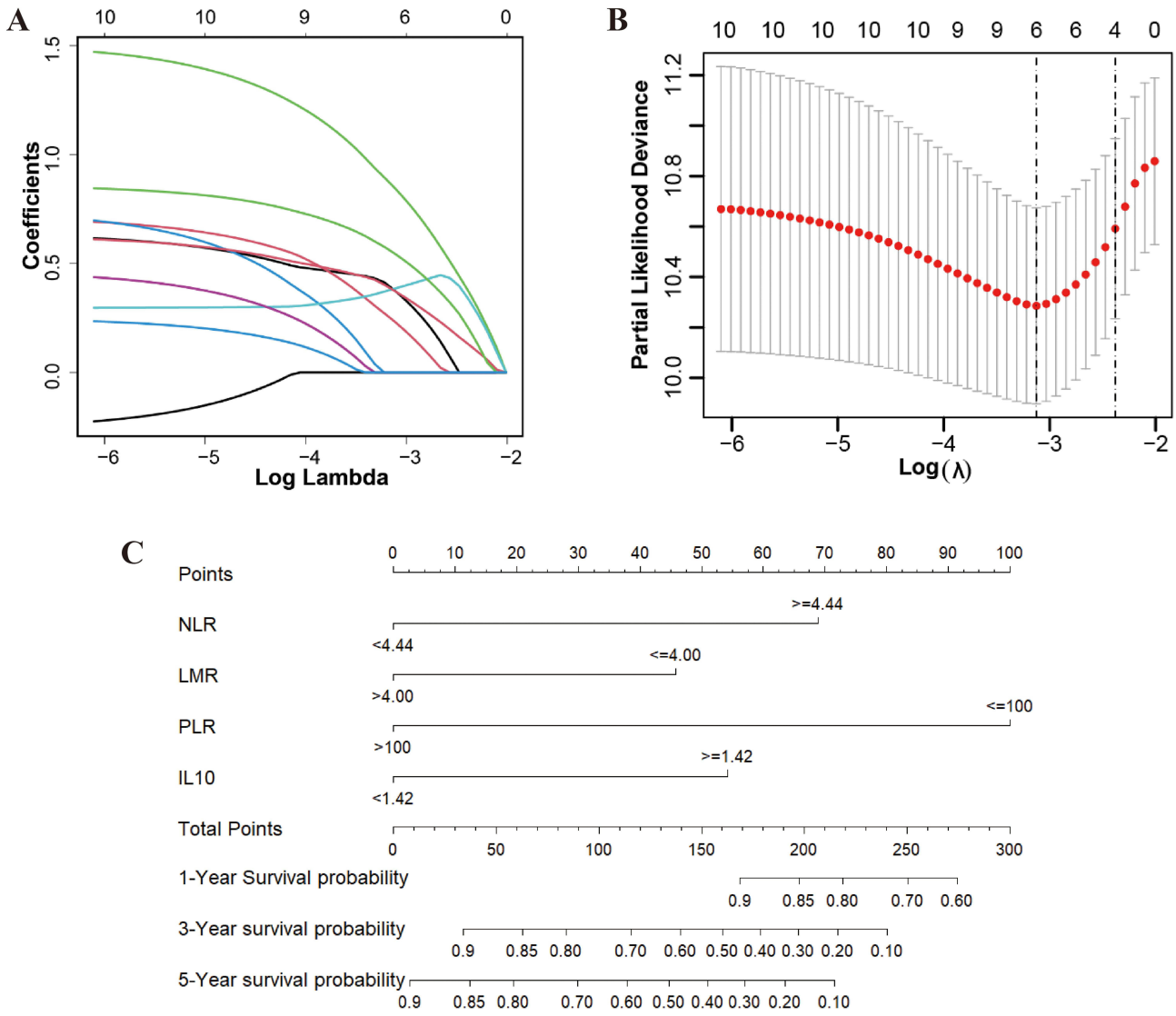

Figure 2 Development of the risk-stratification system based on circulating inflammatory factors. (**A**) The features with nonzero coefficients were selected by optimal lambda. (**B**) The LASSO model was constructed to select the optimal parameters (lambda) and the relationship graph between binomial deviance and log (lambda) was drawn. (**C**) Nomogram model of circulating inflammatory factors.

reflects the body's immune and inflammatory response status. Elevated NLR suggests an imbalance in immune response within the tumor microenvironment; it suppresses the recruitment of immune effector cells to tumor sites, which can foster a beneficial environment for tumor initiation and progression.[27–29] Monocyte-derived cells are important for MM survival and immune evasion.[30] Monocyte-derived cells, including macrophages, myeloid-derived suppressor cells (MDSCs), and dendritic cells (DCs), form an immunosuppressive microenvironment that facilitates the proliferation and survival of MM cells.[21,31] Previous studies have shown that the higher relative number of monocyte-derived cells is associated with poor prognosis in MM patients.[32,33] Shi et al confirmed that MM cells can selectively induce lymphopenia and thrombocytopenia and that a decrease in lymphocytes can lead to an increase in NLR; this means that NDMM patients are often characterized by high NLR. Elevated NLR and decreased LMR are associated with unfavorable characteristic clinical features, and elevated NLR is an independent prognostic factor for progression-free survival (PFS) in NDMM patients.[21] Romano et al confirmed that patients with NLR ≥ 2 have shortener PFS compared to patients with NLR < 2 (22.8 vs 39.7 months, P=0.025), and patients with LMR < 3.6 have inferior PFS to those with LMR ≥ 3.6 (18.5 vs 40.5 months, P=0.0003). These findings highlight the potential of NLR and LMR as predictive markers for PFS in MM patients treated with novel agents as a first-line treatment.[34] Another study also found that reduced LMR was often

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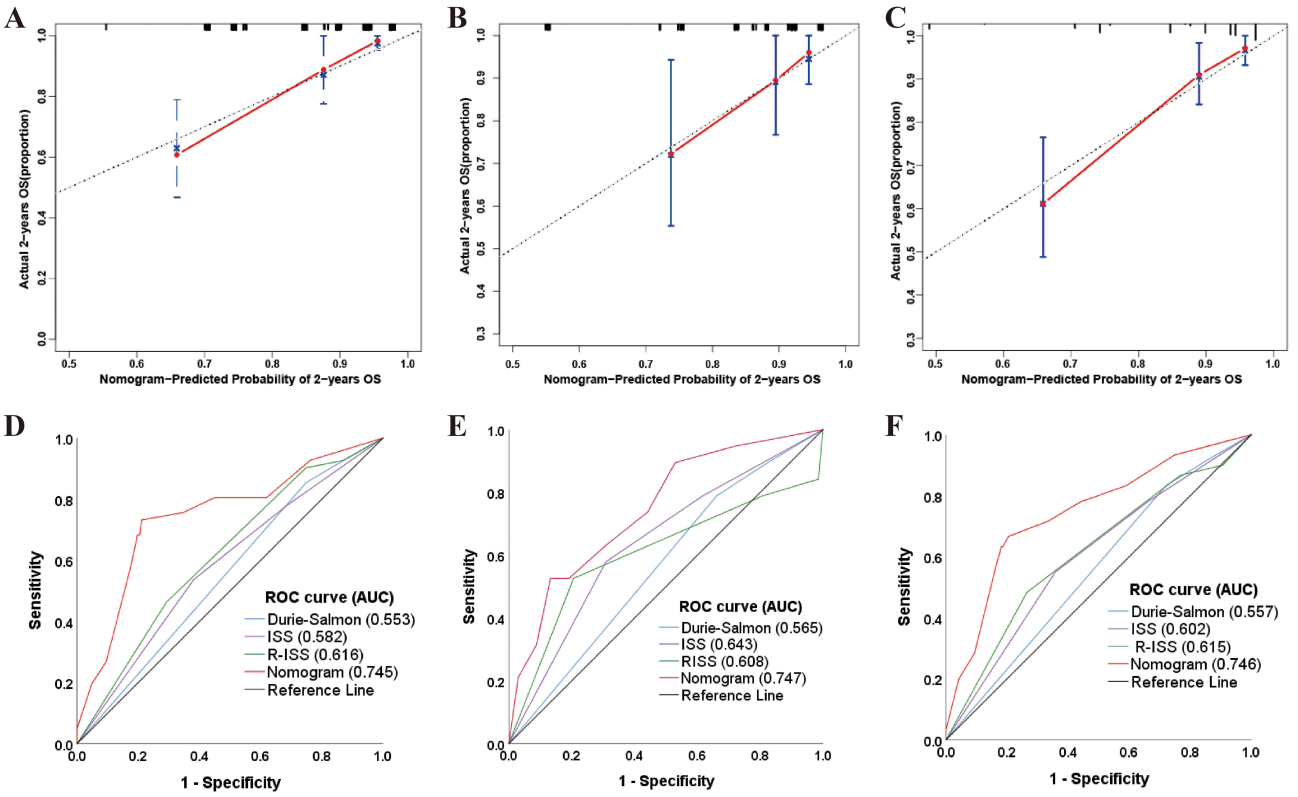

Figure 3 Calibration curves for predicting OS at 2 years and AUCs of the novel risk- stratification system based on circulating inflammatory factors in the training cohort, validation cohort, and entire cohort. (**A**) Predicted vs actually observed probability of 2-year OS in the training cohort. (**B**) Predicted vs actually observed probability of 2-year OS in the validation cohort. (**C**) Predicted vs actually observed probability of 2-year OS in the entire cohort. Area under the ROC curves of nomogram of the novel risk-stratification system based on circulating inflammatory factors, D-S, ISS, and R-ISS stage of OS in the training cohort **(D)**, validation cohort **(E)**, and entire cohort **(F)**.

associated with adverse clinical characteristics of MM patients, such as a higher risk stage, an increased number of bone marrow plasma cells, and lower hemoglobin. Patients with lower LMR at diagnosis had worse median PFS (24 vs 43 months, P<0.001) and OS (48 vs 62 months, P<0.02).[32] Consistent with published studies, our study adds evidence that NLR and LMR can serve as cost-effective and readily available prognostic biomarkers in NDMM patients.

Platelets also participate in inflammatory response, and thrombocytosis is a common characteristic in patients with solid tumors, exerting a significant and adverse impact on prognosis.[21] The PLR has been confirmed to be an active inflammatory marker. In solid tumors, a higher PLR is reported to be associated with poor prognosis, possibly due to an active inflammatory response. However, in MM patients, a lower PLR appears to be associated with poor prognosis.[21,35] This inconsistency may be attributed to the absence of bone marrow involvement in solid tumors, whereas the presence of plasma-cell infiltration in the bone marrow of MM patients seems to dysregulate hematopoiesis.[21,35] In addition to proliferating massively in bone marrow

Table 3 The C-Indices for the Nomogram and the Three Currently Used Staging Systems for Multiple Myeloma to Predict Overall Survival in Patients

Staging systems	Training Cohort		Validation Cohort		Entire Cohort	
	C-index	95% CI	C-index	95% CI	C-index	95% CI
Nomogram	0.777	0.712–0.842	0.714	0.571–0.857	0.710	0.696–0.830
D-S	0.594	0.514–0.674	0.562	0.458–0.666	0.585	0.520–0.649
ISS	0.570	0.482–0.658	0.681	0.551–0.810	0.606	0.533–0.679
R-ISS	0.589	0.501–0.677	0.679	0.541–0.811	0.615	0.542–0.688

Abbreviations: D-S, Durie-Salmon; ISS, international staging systems; R-ISS, revised-ISS; 95% CI, 95% confidence intervals.

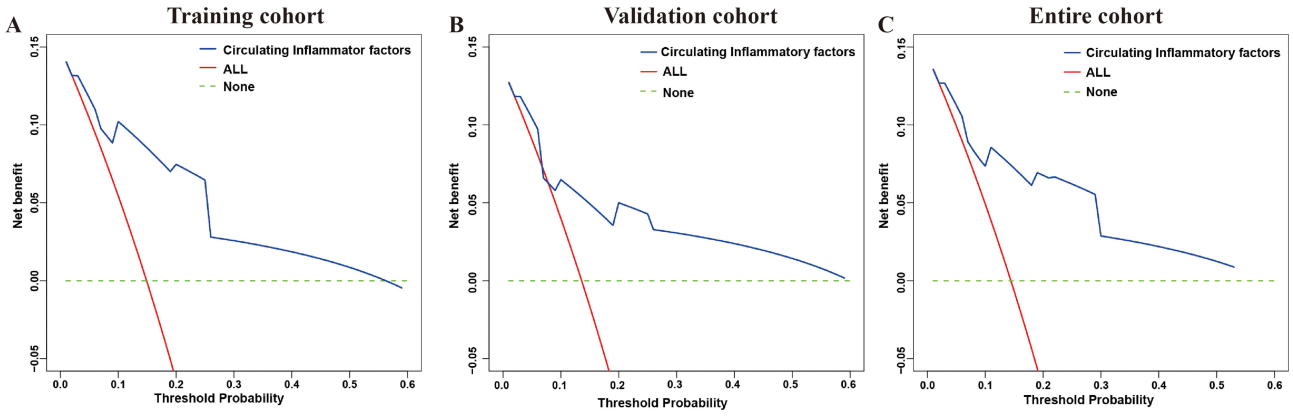

Figure 4 (**A**) The decision-curve analysis (DCA) curve in the training cohort. (**B**) The DCA curve in the validation cohort. (**C**) The DCA curve in the entire cohort.

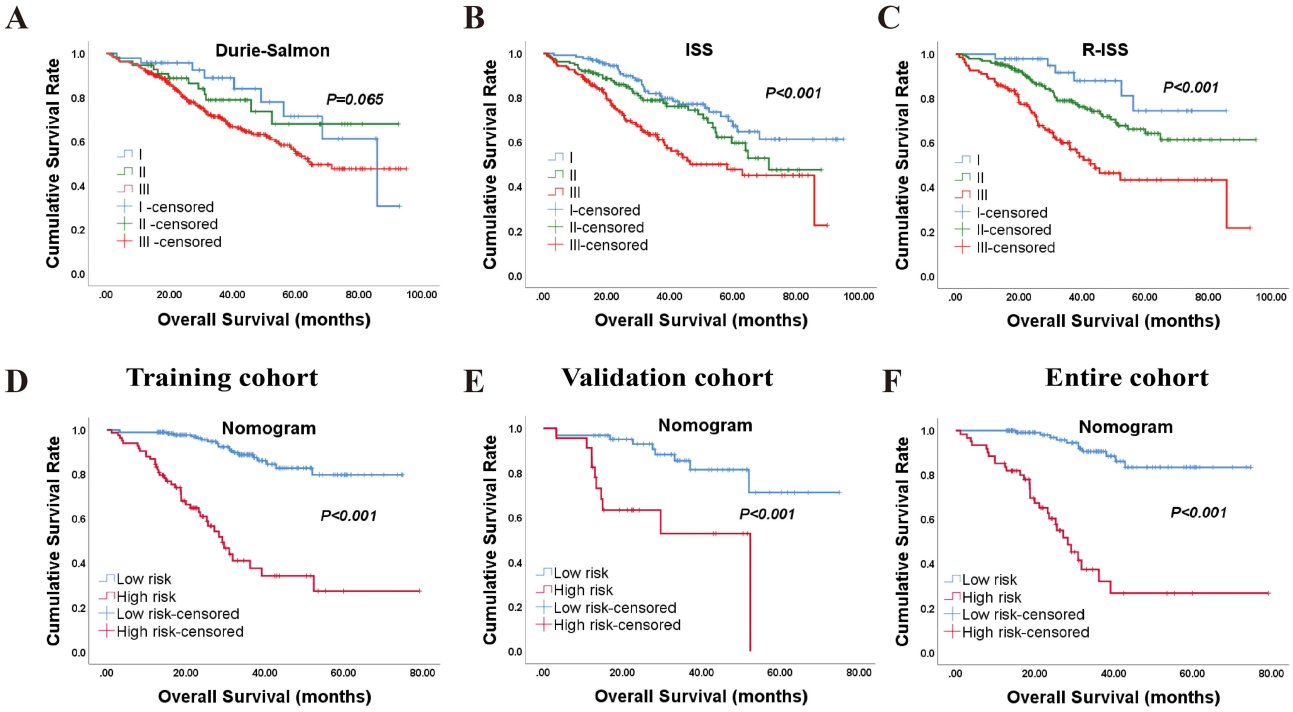

Figure 5 Kaplan-Meier survival curves of the NDMM patients, categorized by different risk-staging systems. (**A-C**) OS of NDMM patients based on D-S (**A**), ISS (**B**), and R-ISS (**C**) risk-stage in the entire cohort. (**D-F**) OS of NDMM patients with high-risk and low-risk according to nomogram of the novel risk-stratification system based on circulating inflammatory factors in the training cohort (**D**), validation cohort (**E**), and entire cohort (**F**).

and suppressing normal hematopoiesis, MM cells also secrete a large amount of hematopoietic inhibitory factors that play an impact on normal hematopoiesis, leading to severe anemia and a significant decrease in platelet numbers. Therefore, PLR serves not only as an inflammatory marker but also as an indicator of MM tumor burden and dysfunction of hematopoiesis.[21,31,35] Studies have shown that decreased PLR is often associated with adverse clinical characteristics of MM, such as a higher risk stage, an increased percentage of bone-marrow plasma cells, lower hemoglobin, and high-risk cytogenetic abnormalities. Decreased PLR is an independent predictor for PFS and OS in NDMM patients,[21,35] which was also confirmed in our results.

IL-10 is a major inhibitor of inflammation in the tumor microenvironment and is mainly secreted by monocytes/macrophages, T lymphocytes, B lymphocytes, natural killer (NK) cells, and mast cells.[36] In addition to serving as an anti-inflammatory and immune-suppressive cytokine that promotes cancer evasion of immune surveillance, IL-10 also can significantly enhance B-cell proliferation, participating in its terminal differentiation into plasma cells.[22] IL-10

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plays roles in various kinds of hematologic malignancies, including chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), and MM.[22,37–39] Multiple studies have confirmed that elevated serum level of IL-10 is significantly associated with adverse clinical features and poor prognosis in MM patients.[19,22,23] Studies have found that serum IL-10 concentration in MM patients is significantly higher than in healthy volunteers, is positively correlated with high-risk disease stages, high β2-microglobulin, LDH levels, and BMPC percentages, and is an independent prognostic factor for PFS and OS in MM patients.[19,22] Our published study also confirmed that serum IL-10 levels are associated with disease progression and high-risk clinical characteristics. Patients with higher serum IL-10 levels exhibit worse PFS (17.7 vs 33.2 months, P=0.040) and OS (28.5 months vs NR, P <0.001) compared to those with lower levels. Furthermore, elevated serum IL-10 has been identified as an independent prognostic factor for OS in NDMM patients.[20] Therefore, serum IL-10 level can also be used as a simple and economical prognostic indicator with significant value for NDMM patients.

These published findings, along with our results, suggest that systemic inflammation markers can be valuable biomarkers for risk stratification and prognosis in MM. Our study confirmed that elevated NLR and IL-10 levels, as well as decreased LMR and PLR, are frequently associated with adverse clinical characteristics in NDMM patients. Additionally, these factors are correlated with poor prognosis and serve as independent adverse prognostic factors for OS in NDMM patients. However, these indicators are scattered and the combined value for prediction of outcomes remains unclear. Therefore, we further established a prognostic system that combined these four inflammatory factors obtained from peripheral blood. Our novel risk-stratification model based on circulating inflammatory factors is proven to have good performance in terms of calibration, discrimination, clinical effectiveness, and improvement in predictive ability, exhibiting promising prognostic value for OS of NDMM patients. This new model can classify NDMM patients into different risk groups and has better discrimination for NDMM patients with different-risk stratification for outcomes than the currently used staging systems.

Circulating inflammatory factors assume a crucial role in the prognostic evaluation of MM, with current staging systems such as the R-ISS presenting definite limitations. Some patients categorized as low-risk in accordance with the R-ISS might encounter adverse prognoses, which could be associated with the patient's inflammatory status. Measuring circulating inflammatory factors such as NLR, LMR, PLR, and IL-10 can provide clinicians with additional information about the patient's prognosis and thus provide guidance when selecting treatment. This risk-stratification model predicated on circulating inflammatory factors can assist physicians in attaining a more real-time and in-depth comprehension of the patient's inflammatory status, thereby enabling the formulation of more individualized treatment decisions. In addition, models based on inflammatory markers can complement existing R-ISS and circulating inflammatory factors to further refine patient prognostic stratification, potentially further improving the predictive efficacy of this system. In conclusion, a model based on circulating inflammatory factors could not only help physicians better understand a patient's inflammatory status, but could also serve as a useful complement to existing staging systems, thus providing additional value in predicting prognosis and selecting treatments. Although our nomogram model performed well in predicting the OS of NDMM patients, our study still suffered from certain limitations. First, it is a single-center retrospective study and lacks external validation using data from other centers, potentially leading to data bias. Second, we had a relatively small sample size, which may lead to overfitting as well as no corrections were made for multiple hypothesis testing. A larger patient population and more sensitive analyses are needed to improve model parsimony and validate our nomogram model. Thirdly, cytogenetic data showed no significant predictive value for OS in our patient cohort, which may suffer from limited sample size, particularly the small number of patients available with cytogenetics data.

Conclusion

In summary, this study established and validated a novel prognostic model integrating circulating inflammatory factors including NLR, LMR, PLR, and IL-10 for NDMM patients. The model is an inexpensive, widely available, and easily interpretable risk-stratification tool, which may complement current risk stratification systems.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University. Informed consent was obtained from all patients to be included in the study.

Consent for Publication

All authors agree with the final version of the manuscript and give their consent for its publication.

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.

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Disclosure

The authors report no conflicts of interest in this work.

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