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Original Article

Integration of clinical features and sociodemographic factors: a simplified prognostic model for patients with multiple myeloma based on a double-center retrospective analysis

Jiaxuan Xu[1*], Ruoyi Wang[1*], Qiaoyan Han[2*], Yifan Zuo[1], Jingjing Sun[1], Bing Chen[1], Xiaoqing Dong[1]

[1]Department of Hematology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, Jiangsu, China; [2]Department of Hematology, Jingjiang People's Hospital, Jingjiang, Jiangsu, China. [*]Equal contributors.

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Abstract: This study aimed to develop and validate a prognostic nomogram that combines clinical and sociodemographic factors of patients with newly diagnosed multiple myeloma (MM). A total of 257 newly diagnosed patients with MM from two independent medical centers in China were included in this retrospective cohort study. Univariate and multivariate Cox regression models were used to identify independent risk factors and to construct the nomogram. The predictive ability of the nomogram was evaluated using the areas under the curve (AUCs) and calibration curves. K-fold cross-validation was employed for internal validation of the nomogram performance. Moreover, a stratification system to determine risk level was generated based on the nomogram. Hemoglobulin, creatinine, rurality, and marital status were significantly associated with overall survival (OS) and were incorporated into the nomogram for OS prediction. The prognostic nomogram showed good discrimination and accuracy, and its predictive capability was superior to the International Staging System. The AUC values predicting the 1-, 3-, and 5-year OS probabilities of the nomogram were 0.775, 0.755, and 0.754, respectively. Subsequently, patients were classified into high- and low-risk subgroups based on the median total points of the nomogram; this risk stratification clearly distinguished between high- and low-risk MM patients with significantly different clinical outcomes (median OS: 27 months vs. 84 months). We established a novel prognostic prediction model by comprehensively incorporating clinical and sociodemographic variables, which can effectively predict the survival outcomes in patients with MM.

Keywords: Multiple myeloma, prognostic model, nomogram, risk stratification, sociodemographic factors

Introduction

Multiple myeloma (MM), which is a malignant monoclonal plasma cell proliferative disease, is the second most common type of hematological malignancy, accounting for 10% of hematological malignancies [1]. Because of the changes in demographics and aging of populations, the incidence of MM is increasing annually in China [2]. Over the past decade, the overall survival (OS) rates of MM patients have significantly improved due to the wide use of newly developed drugs such as proteasome inhibitors (PIs) and immunomodulators, the gradual popularization of hematopoietic stem cell transplantation, and the continuous development of immunotherapy and targeted therapy [3]. However, due to biological heterogeneity and socioeconomic status (SES) disparities, the OS of patients with MM varies greatly [4].

In order to accurately predict the clinical prognosis of patients with MM with different risk levels, commonly used staging systems for MM, such as the International Staging System (ISS), revised ISS (R-ISS), and Durie-Salmon (D-S) staging system, have been widely applied in clinical practice. The ISS and D-S stages are earlier proposed clinical staging systems, which reflect the tumor burden in the early stage of MM, but sometimes demonstrate poor performance in prognosis evaluation [5, 6]. Based on

the ISS stage and the risk of genetic abnormalities, the R-ISS stage was proposed and remains commonly used in the clinic [7]. In-depth research on the prognostic factors of MM has enabled the use of prediction models that combine radiomics features, specific serological markers, comorbidities, or other characteristics, which makes the approaches of prognosis assessment more diverse [8-14].

Disparities in social determinants may partially account for the differences observed in survival outcomes among MM patients with similar characteristics, but existing models only focus on disease-specific clinical features and ignore sociodemographic factors [15, 16]. Socioeconomic levels, including residential area, social support, income level, marital status, insurance status, and other factors, have been associated with long-term prognosis of MM [17-21]. For instance, MM patients with low SES or living in rural areas have poorer survival even compared to those with low tumor burden [15, 20, 22]. This finding could be attributed to the urban-rural gap in medical resources, educational attainment, occupation, among others.

Therefore, to comprehensively evaluate the clinical outcomes of patients with MM, new prediction models incorporating sociodemographic variables should be developed. Nomogram is an integrative and visualized tool that can quantify a predictive model into a numerical estimate of the probabilities of events. It is accurate, simple, and convenient, and is currently applied broadly in the assessment of cancer prognosis. This study aimed to develop and validate a nomogram for predicting survival outcomes for patients with MM based on clinical features and sociodemographic factors.

Materials and methods

Patient selection

In this retrospective study, we enrolled 257 patients with newly diagnosed MM from January 2012 to December 2021 admitted to Jingjiang People's Hospital and Nanjing Drum Tower Hospital. Inclusion criteria were as follows: (a) MM diagnosis was in accordance with the International Myeloma Working Group criteria [23]; (b) complete information regarding treatment regimens; (c) complete data regarding laboratory serum markers; and (d) complete individual-level sociodemographic information. Exclusion criteria were: (a) patients with severe autoimmune disorders; (b) patients who developed second primary malignancies; and (c) patients with a prior history of chemotherapy. Follow-up information was obtained after reviewing the outpatient and inpatient medical records or with phone call interviews. The present study followed the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committees of the Affiliated Drum Tower Hospital of Nanjing University Medical School and Jingjiang People's Hospital.

Variable selection

Clinical and demographic data were collected from patients' medical records. The following clinical information was collected: age at diagnosis, sex, percentage of bone marrow plasma cells (BMPC), levels of albumin (ALB, g/dL), β2-microglobulin (BMG, mg/L), hemoglobin (HGB, g/dL), and creatinine (CREAT, mg/dL), ISS stage, immunoglobulin subtypes, presence of diabetes mellitus, hypertension, and smoking history. Continuous variables (ALB, BMG, HGB, and CREAT) were converted into categorical variables according to clinically meaningful cutoff values. Data on the following sociodemographic characteristics were also obtained: insurance status, employment status, marital status, and rurality. Insurance status was categorized as insured and uninsured. Employment status was divided into employed/retired and unemployed. Marital status was categorized as married and others (including single, divorced, or widowed). Rurality was classified as urban or rural according to patients' place of residence. Therapeutic regimens were divided into two major categories: PI-based and traditional drug-based. Treatment information also included the autologous stem cell transplantation (ASCT) status. The primary survival outcome was OS, which was defined as the time from initial MM diagnosis to death from any cause.

Nomogram construction and validation

Univariate and multivariate Cox regression analyses were performed to identify independent prognostic indicators. Predictors with statistical significance were incorporated to develop a nomogram that could predict 1-, 3-, and 5-year survival probabilities. The area under

Table 1. Baseline demographic and clinical characteristics of MM patients

Characteristics	Results	Percentages
Age (years)		
Median (IQR)	63 (54, 69)	
Range	37-87	
Sex		
Male	148	57.6
Female	109	42.4
Immunoglobulin type		
IgG	106	41.2
IgA	77	30.0
FLC	56	21.8
Other	18	7.0
BMPC (%)		
Median (IQR)	23.5 (10.5, 43.0)	
Range	1.0-92.5	
ALB (g/dL)		
<3.5	138	53.7
≥3.5	119	46.3
BMG (mg/L)		
<5.5	177	68.9
≥5.5	80	31.1
HGB (g/dL)		
<8	97	37.7
≥8	160	62.3
CREAT (mg/dL)		
<1.3	191	74.3
≥1.3	66	25.7
Diabetes mellitus		
Yes	45	17.5
No	212	82.5
Hypertension		
Yes	92	35.8
No	165	64.2
Smoking		
Yes	49	19.1
No	208	80.9
Insurance status		
Insured	132	51.4
Uninsured	125	48.6
Employment status		
Employed/retired	103	40.1
Unemployed	154	59.9
Rurality		
Urban	113	44.0
Rural	144	56.0
Marital status		
Married	232	90.3
Other	25	9.7

the curve (AUC) values of the receiver operating characteristic (ROC) curves were used to evaluate the discriminative performance of the nomogram and other predictive models. Calibration curves were employed to measure the predictive accuracy of the nomogram. Calibration plots were constructed with 1,000 bootstrap resamples to observe errors between actual and predicted survival rates. In addition, a k-fold cross-validation method was applied to verify the performance of the prediction models [24]. The three-fold 666-time and five-fold 400-time cross-validations were employed as an internal validation for the nomogram model. Furthermore, risk scores of all patients were calculated, and the risk level was stratified into two groups according to the median value of the nomogram total points. Kaplan-Meier curves were used to estimate the prognostic effects of the nomogram risk stratification.

Statistical analysis

Baseline characteristics were presented as continuous or categorical variables. Continuous variables were assessed for normality using the Shapiro-Wilk test. Data with non-normal distribution were presented as median with interquartile range (IQR). Survival analyses were performed using the Kaplan-Meier method and log-rank test. Univariate and multivariate Cox proportional hazards models were used to calculate the hazard ratio (HR) and the corresponding 95% confidence interval. All analyses were performed using R software (version 4.0.3). Results were considered statistically significant when the two-tailed *P*-value was below 0.05.

Results

Baseline characteristics of patients with MM

Clinical and demographic characteristics of patients are summarized in **Table 1**. In total, 257 eligible patients with MM were included in this study, of whom 148 (57.6%) were men. Median age was 63 years (range: 37-87). Among the

ISS stage		
I	72	28.0
II	106	41.2
III	79	30.7
Treatment regimens		
PIs-based	203	79.0
Traditional drugs-based	54	21.0
ASCT receipt		
Yes	63	24.5
No	194	75.5

IQR, Interquartile Range; BMPC, Bone Marrow Plasma Cells; ALB, Albumin; BMG, β2-Microglobulin; HGB, Hemoglobin; CREAT, Creatinine; ISS, International Staging System; PIs, Proteasome Inhibitors; ASCT, Autologous Stem Cell Transplantation.

immunoglobulin (Ig) subtypes, IgG showed the highest frequency (41.2%), followed by IgA (30.0%), free light chain (21.8%), and others (7.0%). The median percentage of BMPCs was 23.5% (range: 1.0%-92.5%). With regard to comorbidities, 45 patients had diabetes, while 92 patients had hypertension. Additionally, 132 (51.4%) patients were insured, 103 (40.1%) were employed or retired, 113 (44.0%) were living in urban areas, and 232 (90.3%) were married. According to ISS stage, 28.0%, 41.2%, and 30.7% of patients had stage I, II, and III of the disease, respectively. Moreover, 203 (79.0%) patients received PI-based therapy (bortezomib or carfilzomib), while other patients were treated with traditional drug-based regimens. In addition, 63 (24.5%) patients underwent ASCT.

Survival analysis and nomogram construction

Univariate Cox regression analysis was performed to screen for significant prognostic indicators (**Table 2**). Our results indicated that BMG (P<0.001), HGB (P<0.001), CREAT (P<0.001), employment (P = 0.006), insurance status (P = 0.001), rural residence (P<0.001), marital status (P = 0.001), and ISS stage (P<0.001) were associated with OS in univariate analysis. Kaplan-Meier curve analysis was performed to assess the prognostic value of these factors. Patients with BMG ≥5.5 mg/L (**Figure 1A**), HGB <8 g/dL (**Figure 1B**), or CREAT ≥1.3 mg/dL (**Figure 1C**) had significantly worse prognosis (all P<0.001). Insured status (**Figure 1D**), urban residence (**Figure 1E**), and married status (**Figure 1F**) predicted better prognosis compared with uninsured status, rural residence, and unfavorable marital status, respectively (all P<0.001).

Furthermore, multivariate Cox analysis confirmed that HGB, CREAT, rural residence, and marital status may serve as independent prognostic indicators for OS in patients with MM (**Table 2**). HGB <8 g/dL (P = 0.038), CREAT ≥1.3 mg/dL (P = 0.044), rural residence (P = 0.003), and marital status (P = 0.003) indicated worse survival outcomes in multivariate analysis. A predictive nomogram was constructed to estimate the 1-, 3-, and 5-year survival probabilities (**Figure 2**). The independent prognostic factors (HGB, CREAT, rural residence, and marital status) identified by the Cox regression analysis were incorporated in the nomogram. Different categories of each prognostic factor could be projected based on the matching score; the total score was calculated and plotted in the total points line. Total points corresponded to the three predicted lines of survival outcomes and were used to estimate the 1-, 3-, and 5-year OS rates.

Evaluation and validation of the nomogram

The discrimination ability of the nomogram was assessed using ROC curves. In predicting the 1-year survival (**Figure 3A**), the AUC value of the nomogram was 0.775, which was larger than that of the ISS stage (0.641), HGB (0.649), CREAT (0.705), rural residence (0.635), and marital status (0.547). Similarly, the nomogram AUC values were 0.755 for the 3-year survival (**Figure 3B**) and 0.754 for the 5-year survival (**Figure 3C**), which were superior to those of the other five features. The calibration plots for predicting the 1-, 3-, and 5-year survival probabilities showed that the predicted lines were in close proximity to the actual reference lines (**Figure 4A-C**), which reflected the accuracy and reliability of model predictions.

Moreover, to validate the robustness of our model and avoid overfitting, cross-validation using k-fold values of 3 and 5 was employed for internal verification. As shown in **Table 3**, the three-fold cross-validation (666 times) suggested that the mean AUC values of our nomogram were 0.776, 0.739, and 0.709 for predicting the 1, 3, and 5-year OS probabilities, respectively, which were higher than those of other models. Consistently, the nomogram showed

Table 2. Univariate and multivariate Cox regression analysis of overall survival

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (years)	0.994	0.975-1.013	0.549			
Sex (female vs. male)	0.955	0.644-1.416	0.820			
BMPC (%)	1.004	0.996-1.012	0.338			
ALB (≥3.5 vs. <3.5 g/dL)	0.692	0.467-1.026	0.067			
BMG (≥5.5 vs. <5 mg/L)	2.628	1.724-4.006	<0.001	2.281	0.341-15.246	0.395
HGB (≥8 vs. <8 g/dL)	0.379	0.254-0.565	<0.001	0.593	0.362-0.971	0.038
CREAT (≥1.3 vs. <1.3 mg/dL)	2.331	1.536-3.538	<0.001	1.726	1.015-2.937	0.044
Diabetes mellitus (no vs. yes)	0.976	0.585-1.628	0.926			
Hypertension (no vs. yes)	1.525	0.986-2.359	0.058			
Smoking (no vs. yes)	0.831	0.525-1.316	0.431			
Employment (unemployed vs. employed/retired)	1.788	1.179-2.712	0.006	1.458	0.917-2.318	0.111
Insurance status (uninsured vs. insured)	1.981	1.328-2.956	0.001	1.250	0.793-1.970	0.337
Rurality (rural vs. urban)	2.891	1.880-4.443	<0.001	2.083	1.278-3.397	0.003
Marital status (other vs. married)	2.315	1.384-3.875	0.001	2.297	1.337-3.948	0.003
ISS stage (II vs. I)	1.488	0.893-1.950	0.127	1.313	0.729-2.363	0.364
ISS stage (III vs. I)	3.353	2.482-5.766	<0.001	0.732	0.099-5.386	0.759

BMPC, Bone Marrow Plasma Cells; ALB, Albumin; BMG, β2-Microglobulin; HGB, Hemoglobin; CREAT, Creatinine.

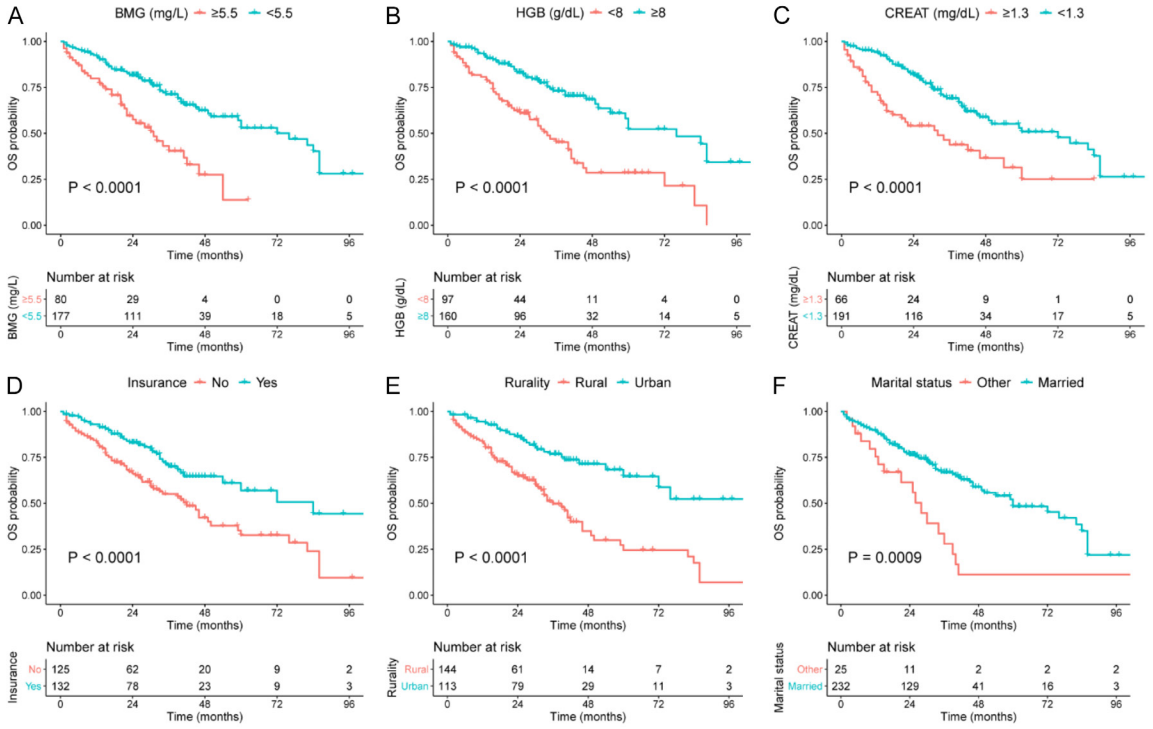

Figure 1. Kaplan-Meier curves for overall survival grouped by (A) BMG (mg/L), (B) HGB (g/dL), (C) CREAT (mg/dL), (D) insurance, (E) rurality, and (F) marital status. BMG, β2-Microglobulin; HGB, Hemoglobin; CREAT, Creatinine.

greater 1-year (0.773), 3-year (0.739), and 5-year (0.703) AUC values than the other five models in the five-fold cross-validation (400 times). These results indicated the good prediction performance of the nomogram.

Comparison between the nomogram and ISS stage

To better predict prognosis of patients with MM, a risk stratification model was established

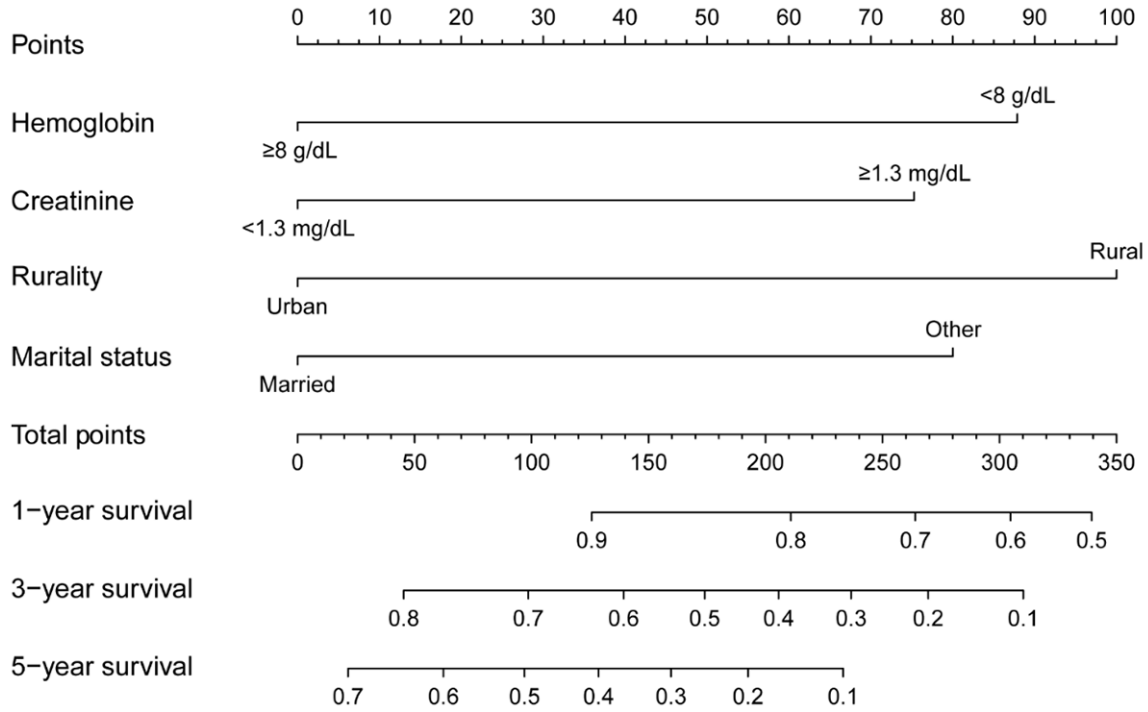

Figure 2. Construction of a nomogram model for predicting 1-, 3-, and 5-year survival.

based on the total points (TP) of the nomogram, and its performance was compared with that of the ISS stage. Using the median risk score (TP: 100) of the nomogram model, patients with a TP over 100 were categorized as the high-risk group, while those with a TP below or equal to 100 were categorized as the low-risk group. Kaplan-Meier curves were used to evaluate the discriminatory ability of the ISS stage and nomogram-based risk stratification. The median OS times of individuals with ISS stage I, II, and III were 76, 54, and 30 months, respectively (P<0.001, **Figure 5A**). Compared with the low-risk group, patients in the high-risk group showed significantly worse survival (median OS time: 27 vs. 84 months, P<0.001, **Figure 5B**).

As presented in **Table 4**, the 1-year OS rates of patients with ISS stages I, II, and III were 94.3%, 89.4%, and 81.0%, respectively; the 1-year OS rates of patients in the low-risk and high-risk groups were 96.3% and 73.4%, respectively. The 3-year OS rates of patients with ISS stage I, II, and III were 77.5%, 67.5%, and 39.0%, respectively; the 3-year OS rates of patients with low-risk and high-risk levels were 77.0% and 34.8%, respectively. The 5-year OS rates of patients with ISS stage I, II, and III were 54.3%, 50.0%, and 25.0%, respectively; the 5-year OS rates of patients with low-risk and high-risk levels were 59.1% and 15.7%, respectively. Overall, risk stratification by nomogram demonstrated better prognosis prediction compared with that of the ISS stage.

Discussion

To provide more insight into the role of sociodemographic factors in the survival of patients with MM, we conducted a two-center retrospective cohort study. We found that rural residence and unfavorable marital status were significantly associated with worse OS in patients with MM. The nomogram established in this study incorporated both disease-specific clinical features and patient-specific sociodemographic factors to predict prognosis of MM patients. The nomogram and risk stratification system exhibited satisfactory results in prognosis prediction and risk assessment.

Our results suggested that marital status and rurality were independent prognostic factors for MM and were, therefore, included into the prognostic model as significant sociodemographic predictors. Marital status was an independent predictor for OS in multiple types of

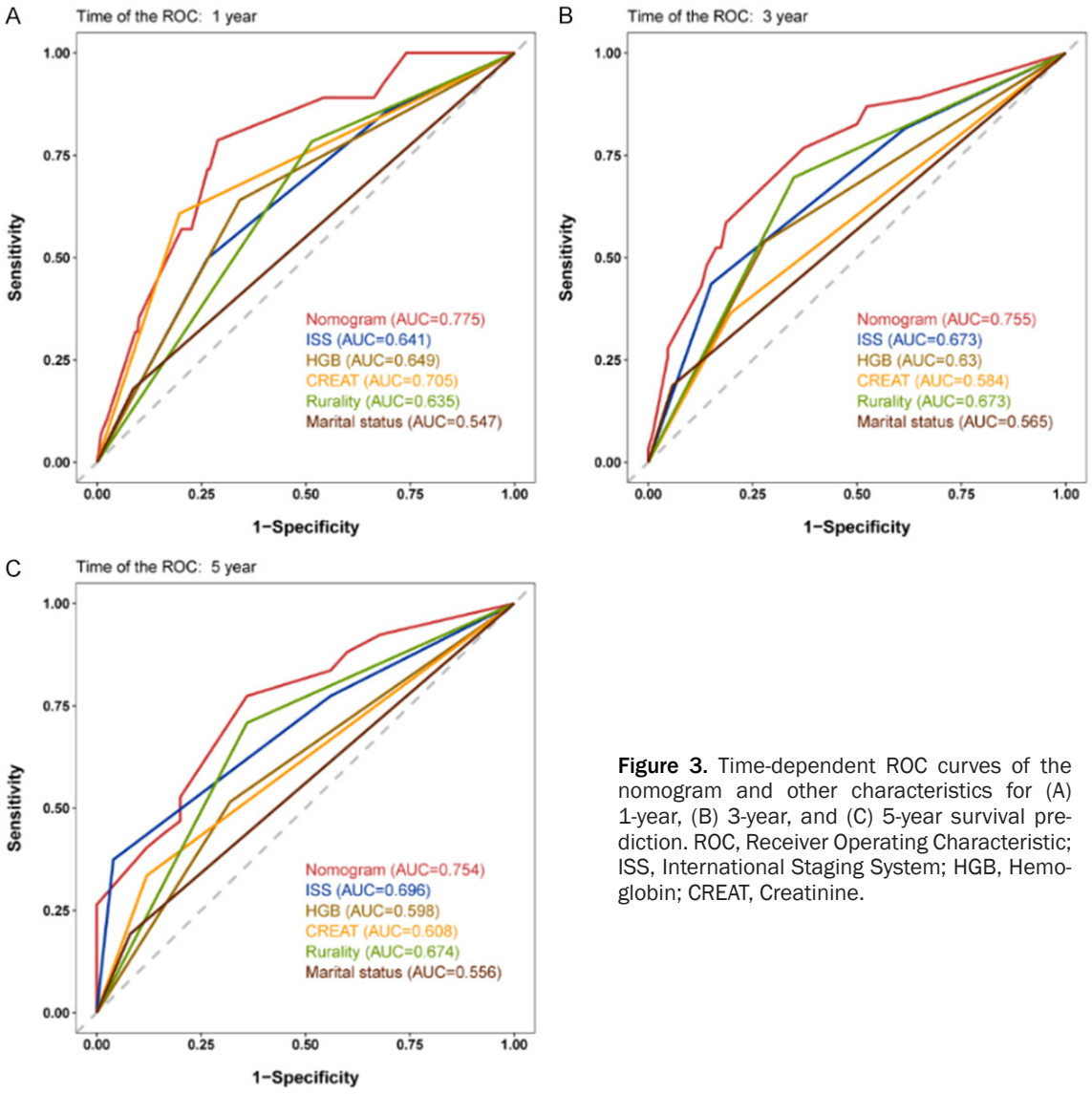

Figure 3. Time-dependent ROC curves of the nomogram and other characteristics for (A) 1-year, (B) 3-year, and (C) 5-year survival prediction. ROC, Receiver Operating Characteristic; ISS, International Staging System; HGB, Hemoglobin; CREAT, Creatinine.

cancer [25-30] as well as in MM, while bad marital status was significantly correlated with poorer survival in MM patients [18, 19]. This could be explained by the chronic psychological stress that results from an unfavorable marital status including divorced, single, and widowed. Stress caused by long-term emotional anxiety, major life events, and insufficient emotional support may accelerate cellular aging and promote tumor progression, which results in shorter survival in patients with cancer [31]. Additionally, patients living in urban areas are likely to have higher survival rates than those living in rural areas. Rural patients tend to face more challenges in accessing high-quality healthcare, sufficient social support, and advanced therapeutic modalities. In contrast, patients living in urban areas are more likely to have easier access to higher-volume facilities and better monitoring and management [32].

We compared several previous nomogram models used in Chinese MM cohorts. Zhang et al. constructed the first nomogram that predicted the survival of patients with MM; however, it was based on single-center data and did not have sufficient discriminative ability [8]. This finding implied the need to incorporate novel factors into the nomogram, in addition to the traditional MM-related prognostic factors. In 2021, Cheng et al. developed two nomograms to predict MM survival: one included circulating

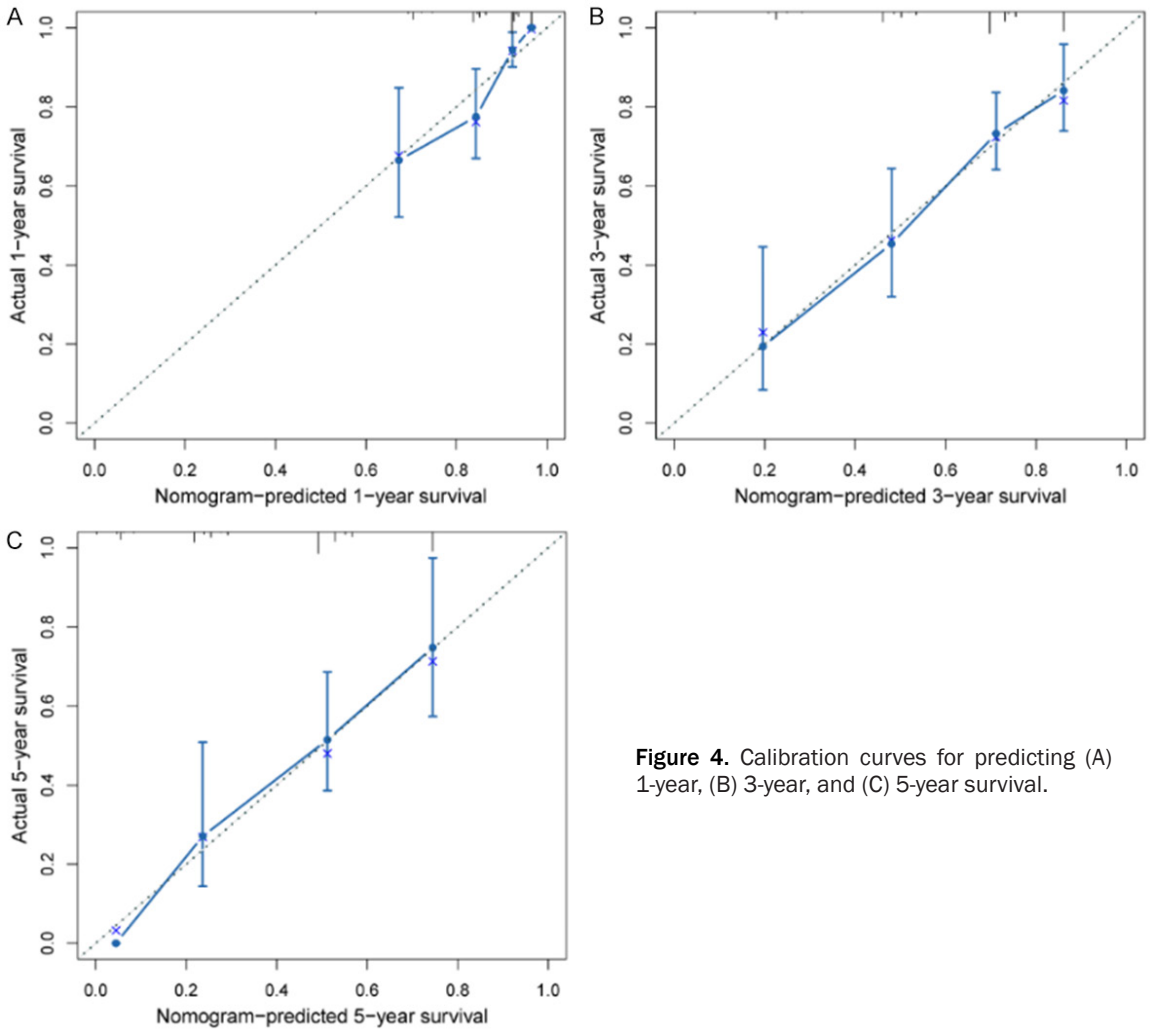

Figure 4. Calibration curves for predicting (A) 1-year, (B) 3-year, and (C) 5-year survival.

Table 3. The mean AUC of the nomogram and other characteristics for prognostic prediction by three-fold and five-fold cross-validations

Characteristics	Three-fold cross-validation			Five-fold cross-validation		
	1-year	3-year	5-year	1-year	3-year	5-year
Nomograms	0.776	0.739	0.709	0.773	0.739	0.703
ISS stage	0.635	0.675	0.665	0.635	0.678	0.665
HGB	0.637	0.634	0.583	0.638	0.635	0.575
CREAT	0.712	0.590	0.613	0.712	0.591	0.614
Rurality	0.638	0.676	0.668	0.638	0.676	0.668
Marital status	0.561	0.572	0.550	0.561	0.572	0.555

AUC, Area Under the Curve; ISS, International Staging System; HGB, Hemoglobin; CREAT, Creatinine.

plasma cells as an independent prognostic marker, and another incorporated cytokine MIP-1α as a new predictor [9, 10]. However, both models were limited by their small patient number, short follow-up time, and single-center design. Moreover, they recognized that low economic level, low insurance status, low education level, and other sociodemographic factors may affect affordability of essential medication and ASCT, which could result in potential bias in survival prediction. Additionally, two independent studies in 2021 incorporated imaging fea-

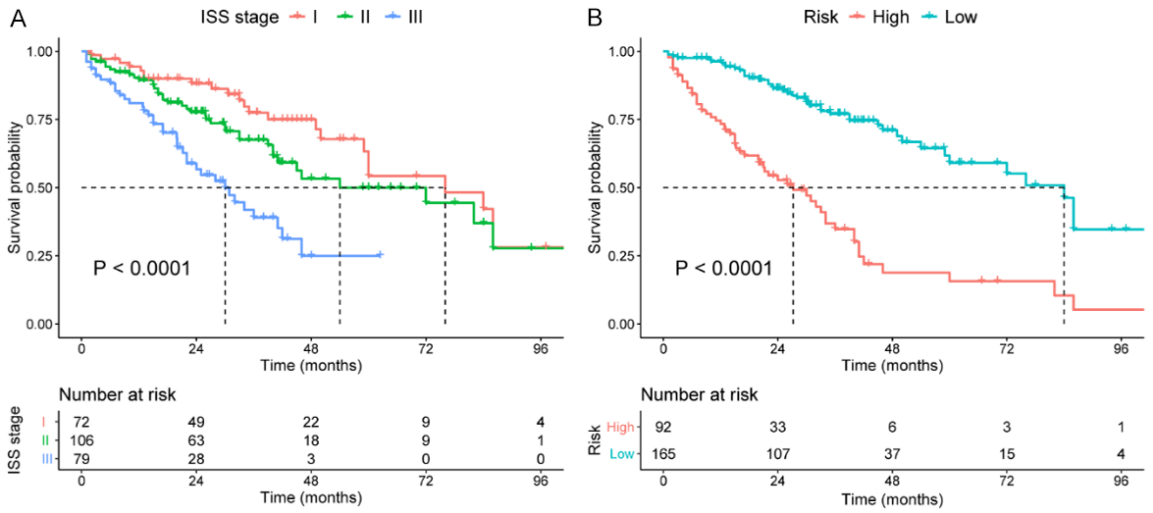

Figure 5. Kaplan-Meier curves for overall survival grouped by (A) ISS stage and (B) nomogram risk stratification.

Table 4. The OS rates and median OS time of patients in different risk groups, stratified by ISS stage and nomogram stratification system

Prognostic models	1-year OS rate	3-year OS rate	5-year OS rate	Median OS
ISS stage				
I	94.3%	77.5%	54.3%	76 months
II	89.4%	67.5%	50.0%	54 months
III	81.0%	39.0%	25.0%	30 months
Nomogram stratification				
Low risk	96.3%	77.0%	59.1%	84 months
High risk	73.4%	34.8%	15.7%	27 months

OS, Overall Survival; ISS, International Staging System.

tures into the nomogram for MM prognosis. Hou et al. used chest computed tomography scanning to assess pleural effusion (PE) and developed a PE-based nomogram to predict the clinical outcomes in unselected MM patients [11]; Li et al. constructed a magnetic resonance imaging-based bone marrow radiomics nomogram for predicting the OS of patients with MM [12]. However, the cost of imaging examination is high, and interpretation of images is equipment-dependent. The evaluation of MM-related imaging scores is somewhat subjective and not as convenient as other laboratory tests.

Compared with the previous nomogram models, our prognostic prediction model has several strengths. First, we collected and analyzed patient data from two independent medical centers in different regions, which allowed extrapolation of our findings and more robust conclusions. In addition, patients were not randomly divided according to a certain proportion; however, three-fold and five-fold cross-validations were performed for robust internal validation, which helped to avoid model overfitting and enhance validation stability. Furthermore, the prognosis of MM patients depends not only on biological and clinical factors but also on socioeconomic characteristics. Compared with previous models that focused only on clinical or molecular factors, our nomogram integrates sociodemographic factors, which allowed for reduced bias in estimating effects.

Although our predictive model performed well in predicting the OS of patients with MM, there were several limitations to this study. First, our sample size was not large enough, which may result in limited statistical power and occasional biases. Hence, future external validation through large-sample and multi-center studies is required to verify the nomogram performance. Second, the present study did not

include adequate clinical variables. Data on the D-S and R-ISS stages were insufficient; therefore, the nomogram model could not be compared with these stage systems. Third, the results of this study were based on Chinese populations; considering the differences in ethnicity and economic levels, further investigation is warranted to determine whether our model may be applicable to patients with MM in other regions or countries.

Conclusion

In summary, our study demonstrated that rurality and marital status are independent sociodemographic predictors for survival differences in MM. Urban and married patients were more likely to have favorable clinical outcomes. Additional research is required to help to prolong survival in patients with low SES levels. Our prognostic nomogram combined both clinical and sociodemographic features, showing good performance in predicting OS; in addition, it performed well on repeated internal validation. Furthermore, our risk stratification model exhibited better discrimination for survival prediction compared with that of the ISS stage, which can precisely evaluate the risk level of each patient with MM.

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Disclosure of conflict of interest

None.

Address correspondence to: Bing Chen and Xiaoqing Dong, Department of Hematology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing 210008, Jiangsu, China. Tel: +86-13951806490; E-mail: chenbing_nju@126.com (BC); Tel: +86-15651015-803; E-mail: qgswns@126.com (XQD)

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