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Original Article

A short-term prognostic model based on urinary IgG, CO_2CP and TP for newly diagnosed multiple myeloma

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Abstract: This study aimed to establish a short-term risk assessment model for patients with newly diagnosed multiple myeloma (NDMM), to augment the current prognosis assessments of MM patients. This model serves as a reference for evaluating the short-term remission of patients. Between January 2013 and March 2023, a total of 232 NDMM patients were enrolled in the Hematology department. The cohort between January 2013 and October 2020 was selected as the training set (n=165) and the cohort between November 2020 and March 2023 was used as the internal validation set (n=67). Using univariate and multivariate forward stepwise Cox analysis, the determined prognostic factors were urinary immunoglobulin G (IgG), carbon dioxide combining power (CO_2CP), and total protein (TP). A 3-prognostic factor Nomogram model was established based on Cox regression. The area under the curve (AUC) of the Nomogram in 4-, 5- and 6-month complete remission (CR) was 0.777, 0.722, and 0.708, and the C index was 0.691 (0.661-0.721). Kaplan-Meier curve analysis indicated that the CR rate of the high-risk group was lower than the low-risk group (training set P<0.001, internal validation set P=0.018), which exhibited a better stratification of patients than the International Staging System (ISS, training set P=0.850, internal validation set P=0.900), Revised International Staging System (R-ISS, training set P=0.740, internal validation set P=0.720) and the Second Revision of the ISS (R2-ISS, training set P=0.480, internal validation set P=0.590). This study effectively constructed a Nomogram for short-term risk assessment of NDMM patients based on three widely used clinical markers, thereby enriching factors related to NDMM prognosis and aiding in the evaluation of the short-term complete remission.

Keywords: Multiple myeloma, prognostic model, urinary immunoglobulin G, carbon dioxide combining power, total protein

Introduction

Multiple myeloma (MM) is a malignant tumor characterized by abnormal proliferation of cloned plasma cells in the bone marrow and accounts for approximately 10% of hematologic malignancies [1, 2]. Globally, multiple myeloma has been diagnosed in over 155,688 people, and approximately 100,000 people die from the disease annually [3]. MM is a highly heterogenous disease and sustained complete remission is difficult to achieve for some patients despite the improvements that have been made in the past 20 years by some novel drugs on the overall survival rate of patients [4]. The risk stratification system for multiple myeloma has been updated regularly by the International Myeloma Working Group (IMWG). The current system primarily consists of the International Staging System (ISS) [5], Revised ISS (R-ISS) [6], and Second Revised of ISS (R2-ISS) [7]. These systems, however, do not account for patients with additional cytogenetic abnormalities or related variables like nutrition and performance status, which causes differing results in high-risk patients [2, 8, 9]. The Mayo Clinic published consensus guidelines [10] in 2013 that state that NDMM patients' response to 4-cycle chemotherapy and their level of risk determine whether or not they

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should receive autologous hematopoietic stem cell transplantation. However, prognostic studies on MM remission following short-term chemotherapy are comparatively scarce.

The reasons mentioned above have led to the ongoing requirement for new research to investigate host-related factors and create risk stratification. In addition to other biological markers in MM, such as inflammatory and nutritional parameters, these studies established prognostic cut-off values and tools [11-14]. Ren et al found that System Inflammation Response Index (SIRI) >0.87 and Platelet-Lymphocyte Ratio (PLR) ≤ 106.44 were risk factors for prognosis in NDMM patients [2]. Zhang et al's meta-analysis also suggested that increased Neutrophil-Lymphocyte Ratio (NLR) was significantly associated with poor outcomes in MM patients, and increased Lymphocyte-Monocyte Ratio (LMR) predicted better outcomes, while the prognostic significance of PLR was not confirmed [15]. Moreover, Li et al's study highlighted that the elderly adults with poor Controlling Nutritional Status (CONUT) and Prognostic Nutritional Index (PNI) score assessment were more likely to develop MGUS [12]. Furthermore, a model integrating serum lipid profile was developed to predict the prognosis of multiple myeloma (MM) by utilizing triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), lactate dehydrogenase (LDH), apolipoprotein B (ApoB), and ApoB/apolipoprotein A1 (ApoA1) ratios [16]. Nevertheless, little is known about the prognostic value of these indicators in short-term remission after chemotherapy in MM.

A nomogram is a graphical representation of a complex mathematical formula in the form of lists and lines [17]. There are primarily two types. The first is the static graphic method, which creates a scale line segment with a specific assignment based on the independent variable's regression coefficient. It then integrates this data into a graph and calculates the result based on the total score. The second is the dynamic formula method, which allows for the direct entry of the formula into a computer or mobile device calculator and receives the predicted result.

Therefore, based on the evidence of indicators we mentioned above, our study aimed to explore the prognostic value of inflammatory, nutritional parameters, serum lipid profile, and other indicators for predicting short-term complete remission (CR) in patients with NDMM. We established a novel simple Nomogram to predict short-term outcomes in NDMM patients, as a supplement for current risk classifications.

Materials and methods

Study patient selection

We retrospectively reviewed recorded patients of NDMM in the Hematology Department of Guangdong Provincial People's Hospital from January 2013 to March 2023 through the hospital information system. The inclusion criteria were as follows: (1) Patients newly diagnosed with MM in Guangdong Provincial People's Hospital. (2) Patients who received regimens containing at least 4 cycles. (3) Patients with complete laboratory data. (4) Patients without other serious autoimmune diseases. This retrospective study followed the principles of the Declaration of Helsinki and was approved by the Medical Ethics Committees of Guangdong Provincial People's Hospital (the ethical approval number: KY-Q-2022-110-01).

Clinical data collection and study endpoints

The baseline characteristics were collected, such as clinical, laboratory data and remission information. Clinical data involved gender, age, time of admission, ISS stage, R-ISS stage, R2-ISS stage, last follow-up, as well as initial therapy and response of treatment. Complete laboratory data included neutrophil granulocyte (NEU), lymphocyte (LYM), monocyte (MONO), hemoglobin (HGB), platelet (PLT), blood urea nitrogen (BUN), carbon dioxide combing power (CO_2CP), uric acid (UA), serum calcium (Ca^{2+}), serum β2-microglobulin (β2-MG), lactic dehydrogenase (LDH), total protein (TP), albumin (ALB), globulin (GLO), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), urinary immunoglobulin G (IgG), urinary transferrin (TF), urinary β2-MG. Additionally, patient data from Fluorescence in Situ Hybridization (FISH) was collected; these data included 13q deletion, 17p deletion, IGH rearrangement, and 1q gain [18]. All clinical laboratory results above were measured before the initiation of chemotherapy.

NLR, PLR, LMR, SIRI, SII were calculated as follows [2, 14]: NLR = NEU (10^9/L)/LYM (10^9/L); PLR = PLT (10^9/L)/LYM (10^9/L); LMR = LYM (10^9/L)/MONO (10^9/L); SIRI = NEU (10^9/L) × MONO (10^9/L)/LYM (10^9/L); SII = NEU (10^9/L) × PLT (10^9/L)/LYM (10^9/L). Corrected serum calcium (CCA), PNI, HALP were calculated as follows [19-21]: CCA = serum Ca^{2+} (mmol/L) - 0.025 × ALB (g/L) + 1.0; PNI = ALB (g/L) + 5 × LYM (10^9/L); HALP = HGB (g/L) × ALB (g/L) × LYM (10^9/L)/PLT (10^9/L). CONUT scores were determined by ALB (g/L), TC (mmol/L), and LYM (10^9/L) [9, 12, 22].

In this study, patients with NDMM were followed up through regular outpatient and inpatient visits, and the primary follow-up outcome was to evaluate the remission status of patients after 4 cycles of chemotherapy. The final follow-up was conducted on March 31, 2023. Short-term complete response (CR), which is measured as the duration between the time of diagnosis and the completion of four treatment cycles, was the main endpoint. The complete response of MM was assessed by serum, urine immunofixation electrophoresis, bone marrow plasma cell ratio, serum free light chain, and radiologic imaging findings [23].

Cut-off values for prognostic parameters

The optimal cut-off values of the above potential prognostic variables were determined based on maximally selected rank statistics (R package "maxstat") for CR [24]. Thus, the continuous variables were transferred into categorical variables, and patients were stratified into low- and high-level sub-groups based on the cut-off values. Variables above and below the optima cut-off values were scored as 1 and 0, respectively.

Statistical analysis

Baseline characteristics were presented as continuous (mean ± SD) or categorical variables (n/%). Continuous variables were assessed for normality using the Shapiro-Wilk test. Data with non-normal distribution were presented as median with interquartile range (IQR). Uni- and multivariable Cox proportional hazard models were used to assess the prognostic factors and calculated hazard ratios (HR) with 95% confidence intervals (CI). All the statistical analyses were carried out using R version 4.3.1 and SPSS version 25.0, and a two-sided P<0.05 suggested a statistical significance.

Results

Baseline characteristic

A total of 232 eligible patients with NDMM between January 2013 and March 2023 were enrolled in this study. These patients were divided into the training set (n=165) and internal validation set (n=67) at a ratio of 7:3 as shown in **Figure 1**.

The baseline patient characteristics are presented in **Table 1**. A total of 122 patients (52.6%) were male. The median age at diagnosis for all patients was 61 years (IQR: 53-67), and 122 patients (52.6%) were older than 60 years. According to three stages, stage III ISS was noted in 105 patients (45.3%), 119 patients (51.3%) were stage II R-ISS and 122 patients (52.6%) were stage III R2-ISS. A total of 108 patients (46.6%) had moderate to severe nutritional status (CONUT score ≥5). Most patients (143, 61.6%) exhibited abnormal FISH. The baseline characteristics were comparable and well-balanced between the two sets.

Short-term prognostic variables identification

The results of the univariate and multivariate Cox analyses are illustrated in **Figure 2** and Table S2. Univariate Cox analysis indicated that high urinary IgG, high urinary TF, low CO_2CP, low PNI, high TP, and high GLO were associated with a poorer CR (P<0.05). While multivariate Cox forward stepwise analysis showed that high urinary IgG, low CO_2CP, and high TP were independent prognostic factors (P<0.05).

In addition, we utilized the Kaplan-Meier curve analysis to compare the levels of urinary IgG, CO_2CP, and TP at low and high levels. Patients with higher urinary IgG levels (≥7.93) exhibited a better CRR than those with lower urinary IgG levels (<7.93) (P<0.001, **Figure 3A**). Significant differences between the patient curves divided by CO_2CP and TP (P=0.004; P<0.001, **Figure 3B**, **3C**) were observed.

Construction and evaluation of the Nomogram

Using the three independent prognostic factors (urinary IgG, CO_2CP and TP) mentioned above, a

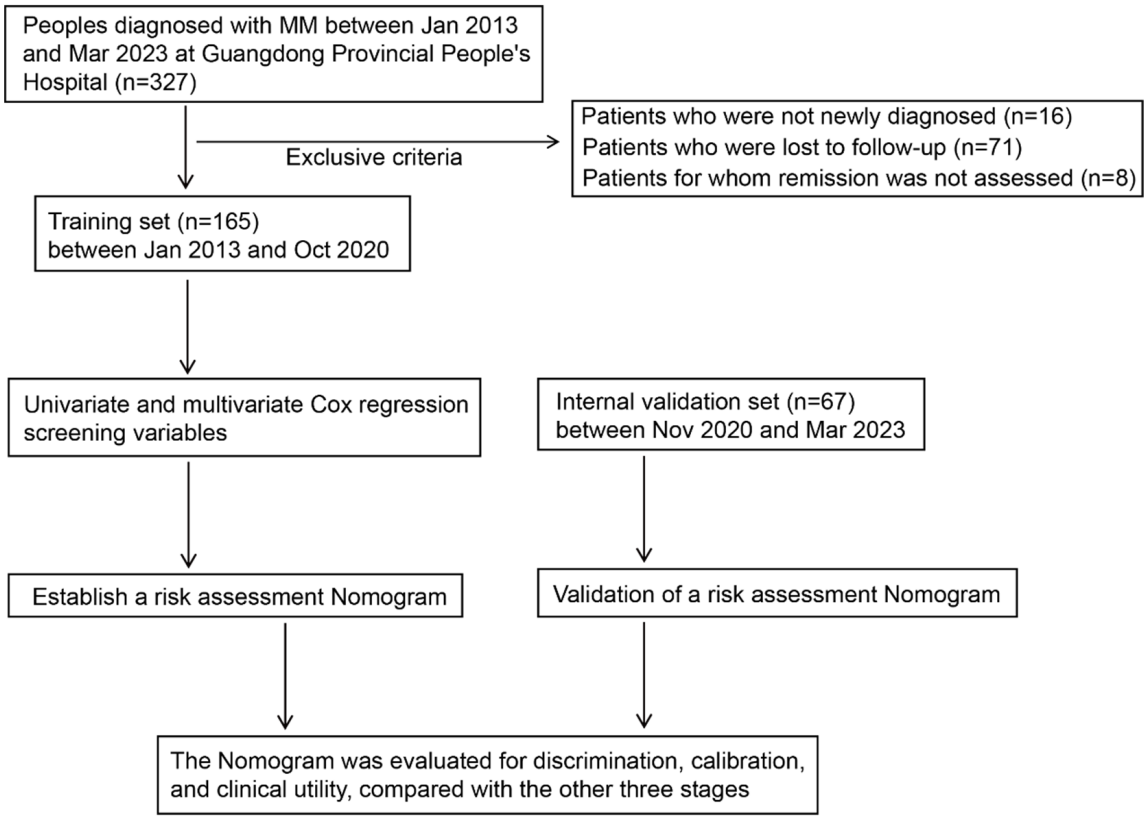


Figure 1. The inclusion process of MM and flow chart of establishing model.

Table 1. Baseline characteristics of training set and internal validation set

Characteristics	Training set (n=165)	Internal validation set (n=67)	P
Sex [n (%)]			0.511
Male	84 (50.91)	38 (56.72)	
Female	81 (49.09)	29 (43.28)	
Age (years)	61 (52, 67)	59 (53.5, 67)	1.000
ISS stage [n (%)]			0.335
ISS I	26 (15.76)	16 (23.88)	
ISS II	63 (38.18)	22 (32.84)	
ISS III	76 (46.06)	29 (43.28)	
R-ISS stage [n (%)]			0.126
R-ISS I	24 (14.55)	16 (23.88)	
R-ISS II	84 (50.91)	35 (52.24)	
R-ISS III	57 (34.55)	16 (23.88)	
R2-ISS stage [n (%)]			0.341
R2-ISS I	16 (9.7)	12 (17.91)	
R2-ISS II	35 (21.21)	15 (22.39)	
R2-ISS III	90 (54.55)	32 (47.76)	
R2-ISS IV	24 (14.55)	8 (11.94)	
Urinary IgG (mg/L)	7.93 (3, 42.1)	9.24 (4.57, 22.85)	0.861
Urinary TF (mg/L)	2.47 (2, 8.75)	2.92 (1.16, 15.15)	0.608
Urinary β2-MG (mg/L)	0.91 (0.28, 12.4)	0.94 (0.2, 14.1)	0.674

BUN (mmol/L)	6.1 (4.8, 8.56)	6.54 (5.44, 12.09)	0.069
CO_2CP (mmol/L)	23.9 (21.8, 26)	23.5 (20.65, 25.6)	0.189
UA (μmol/L)	456 (369, 568.3)	444.5 (378.5, 568.4)	0.755
Serum β2-MG (mg/L)	4.91 (3.44, 11.2)	4.84 (2.88, 9.75)	0.353
CCA (mmol/L)	2.46 (2.33, 2.62)	2.43 (2.35, 2.59)	0.804
NLR	2.05 (1.35, 3.12)	2.01 (1.28, 2.62)	0.435
PLR	116.97 (76.54, 172.9)	119.46 (71.81, 155.98)	0.289
LMR	3.25 (2.43, 4.7)	3.44 (2.55, 4.8)	0.428
SIRI	1.04 (0.53, 1.65)	1.01 (0.59, 1.59)	0.654
SII	372.76 (209.37, 711.74)	367.2 (206.52, 578.12)	0.361
HALP score	22.96 (13.58, 35.5)	28.35 (20.01, 38.96)	0.014
PNI	40.12 ± 8.26	42.81 ± 7.21	0.015
CONUT score [n (%)]			0.012
Normal and mild	79 (47.88)	45 (67.16)	
Moderate and severe	86 (52.12)	22 (32.84)	
LDH (U/L)	184 (151, 254)	164 (132.5, 217.5)	0.080
TP (g/L)	85.2 (69.2, 108.9)	79.5 (66.05, 109.44)	0.610
ALB (g/L)	31.42 ± 7.68	33.51 ± 6.76	0.043
GlO (g/L)	54.3 (32.2, 81.9)	45.5 (27, 79.9)	0.413
TC (mmol/L)	3.8 (2.8, 4.7)	3.82 (2.86, 5.18)	0.616
TG (mmol/L)	1.22 (0.91, 1.88)	1.24 (0.98, 1.81)	0.875
HDL-C (mmol/L)	0.87 (0.69, 1.12)	0.90 (0.74, 1.14)	0.506
LDL-C (mmol/L)	2.25 (1.42, 3.04)	2.45 (1.62, 3.16)	0.302
del(13q) [n (%)]			0.152
No	114 (69.09)	39 (58.21)	
Yes	51 (30.91)	28 (41.79)	
del(17p) [n (%)]			0.769
No	155 (93.94)	62 (92.54)	
Yes	10 (6.06)	5 (7.46)	
IGH rearrangement [n (%)]			0.036
No	121 (73.33)	39 (58.21)	
Yes	44 (26.67)	28 (41.79)	
1q+ [n (%)]			0.540
No	97 (58.79)	43 (64.18)	
Yes	68 (41.21)	24 (35.82)	
FISH [n (%)]			0.211
Normal	68 (41.21)	21 (31.34)	
Anormal	97 (58.79)	46 (68.66)	

TF, Transferrin; β2-MG, β2-microglobulin; BUN, Blood Urea Nitrogen; CO_2CP, Carbon Dioxide Combing Power; UA, Uric Acid; CCA, Corrected Serum Calcium; NLR, Neutrophil-Lymphocyte Ratio; PLR, Platelet-Lymphocyte Ratio; LMR, Lymphocyte-Monocyte Ratio; SIRI, Systemic Inflammation Response Index; SII, Systemic Immune Inflammation Index; HALP score, Hemoglobin Albumin Lymphocyte and Platelet score; PNI, Prognostic Nutritional Index; CONUT score, Controlling Nutritional Status score; LDH, Lactic Dehydrogenase; TP, Total Protein; ALB, Albumin; GLO, Globulin; TC, Total Cholesterol; TG, Triglycerides; HDL-C, High Density Lipoprotien Cholesterol; LDL-C, Low Density Lipoprotien Cholesterol; del(13q), 13q Deletion; del(17p), 17p Deletion; 1q+, 1q Gain; FISH, Fluorescence in Situ Hybridization.

short-term Nomogram was generated for each patient. The Nomogram can predict CR at 4-, 5-, and 6-month intervals (**Figure 3D**); a higher total score indicated a worse CR.

The AUCs for 4-, 5-, and 6-month CR in the training set were 0.777, 0.722, and 0.708, respectively (**Figure 4A**). In the training set, the 50-sample bootstrapped calibration curve,

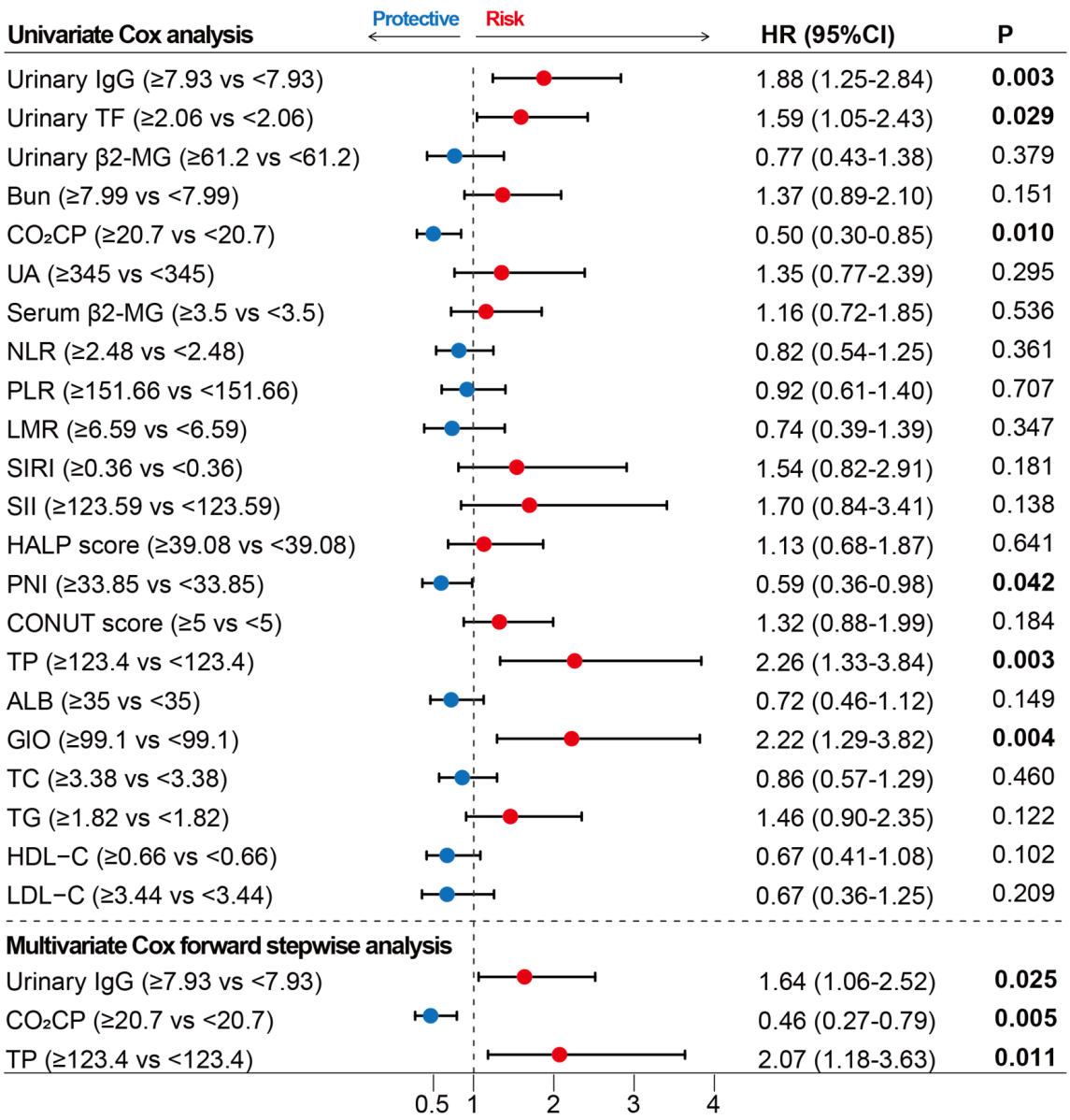


Figure 2. Univariate (top) and multivariate (bottom) Cox analysis of training set.

with 1,000 bootstrap resamples, was used to examine the calibration of the Nomogram. The estimated 6-month CR probabilities were consistent with those found in 6-month CR (**Figure 4C**). The Nomogram outperformed the other MM staging systems in the training set in terms of accuracy, as shown by time-dependent AUC and C-index curves (P<0.001, **Figure 4E** and **4G**; Table S1).

We also calculated the total score for the training set according to the Nomogram and divided them into low-, and high-risk groups according to the median scores. Next, the Kaplan-Meier curve analysis suggested that the Nomogram stratification performed better in identifying a specific group of high-risk patients (P<0.001, **Figure 5A**), while other MM staging systems were not satisfactory in stratifying patients (P=0.850, P=0.740, P=0.480, **Figure 5C**, **5E**, **5G**).

Internal validation of the Nomogram

Furthermore, the Nomogram was validated using the internal validation set. The AUC of the

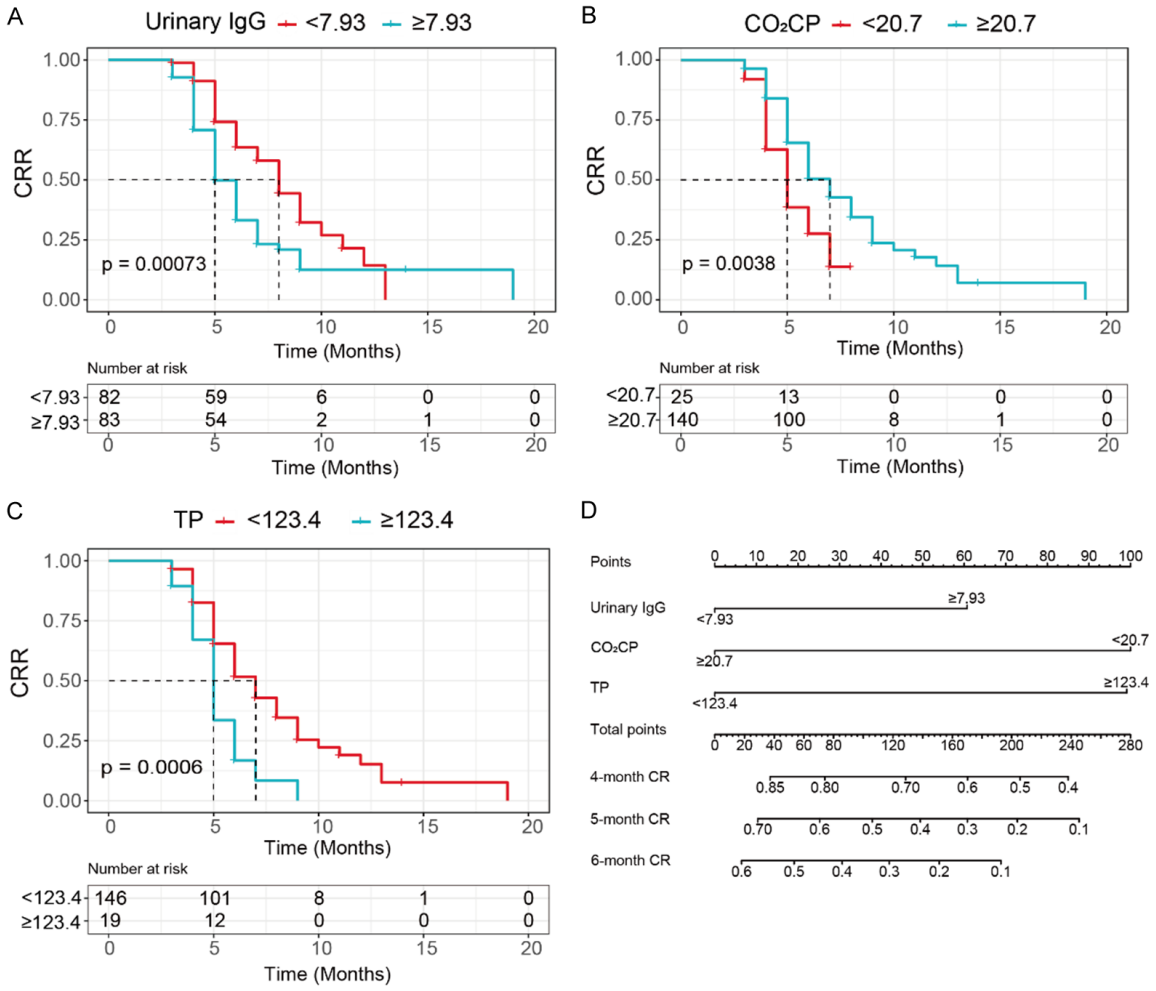


Figure 3. Kaplan Meier curve of urinary IgG, CO_2CP and TP, and Nomogram plot. A. Urinary IgG<7.93 mg/L vs ≥7.93 mg/L. B. CO_2CP<20.7 mmol/L vs ≥20.7 mmol/L. C. TP<123.4 g/L vs ≥123.4 g/L. D. Short-term prognostic Nomogram plot was established based on urinary IgG, CO_2CP and TP.

Nomogram model for 4-, 5-, and 6-month CR were 0.515, 0.608, and 0.642, respectively (**Figure 4B**) in the internal validation sets. The calibration curves of the Nomogram showed a 6-month CR that was graphically consistent with the observed findings (**Figure 4D**). The 5-month CR AUC of the Nomogram was higher than those of the other stages (ISS, R-ISS, and R2-ISS stage) in the time-dependent AUC curve (**Figure 4F**), indicating a better prediction performance. However, the Nomogram's AUC value for other time CR was unsatisfactory. Time-dependent C-index curves also revealed that the Nomogram was significantly higher than the other three stages (P<0.001, **Figure 4H**; Table S1).

In addition, the Kaplan-Meier curve of the Nomogram also showed a greater short-term risk stratification (P=0.018, **Figure 5B**), while those of the other stages were superimposable and not enough for predicting short-term CR (P=0.900, P=0.720, P=0.590, **Figure 5D**, **5F**, **5H**). Based on these findings, we concluded that the Nomogram can be used to predict the short-term prognosis of NDMM patients due to its dependable reproducible results.

Subgroup analyses

Subsequently, we investigated the Nomogram stratification performance in two distinct patient groups from the training set: aged <70

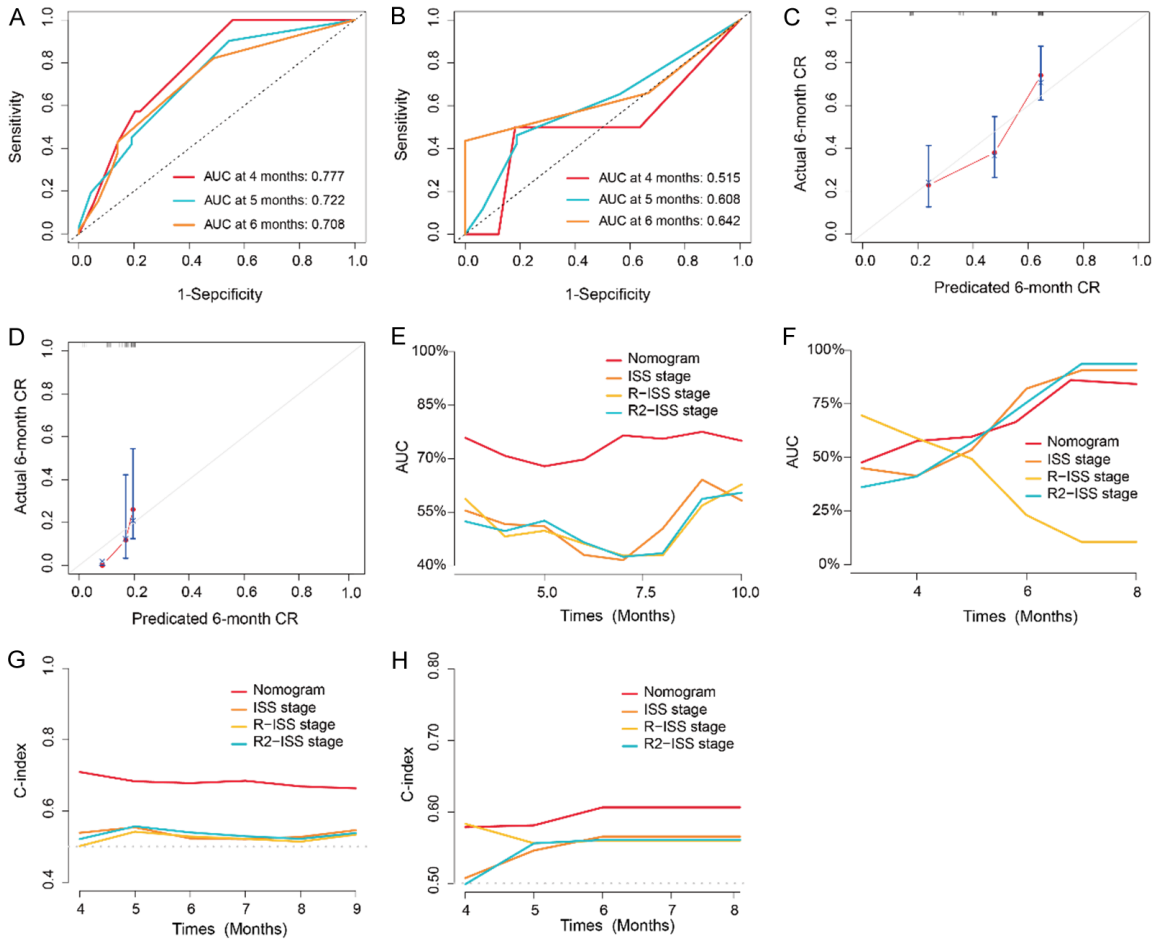


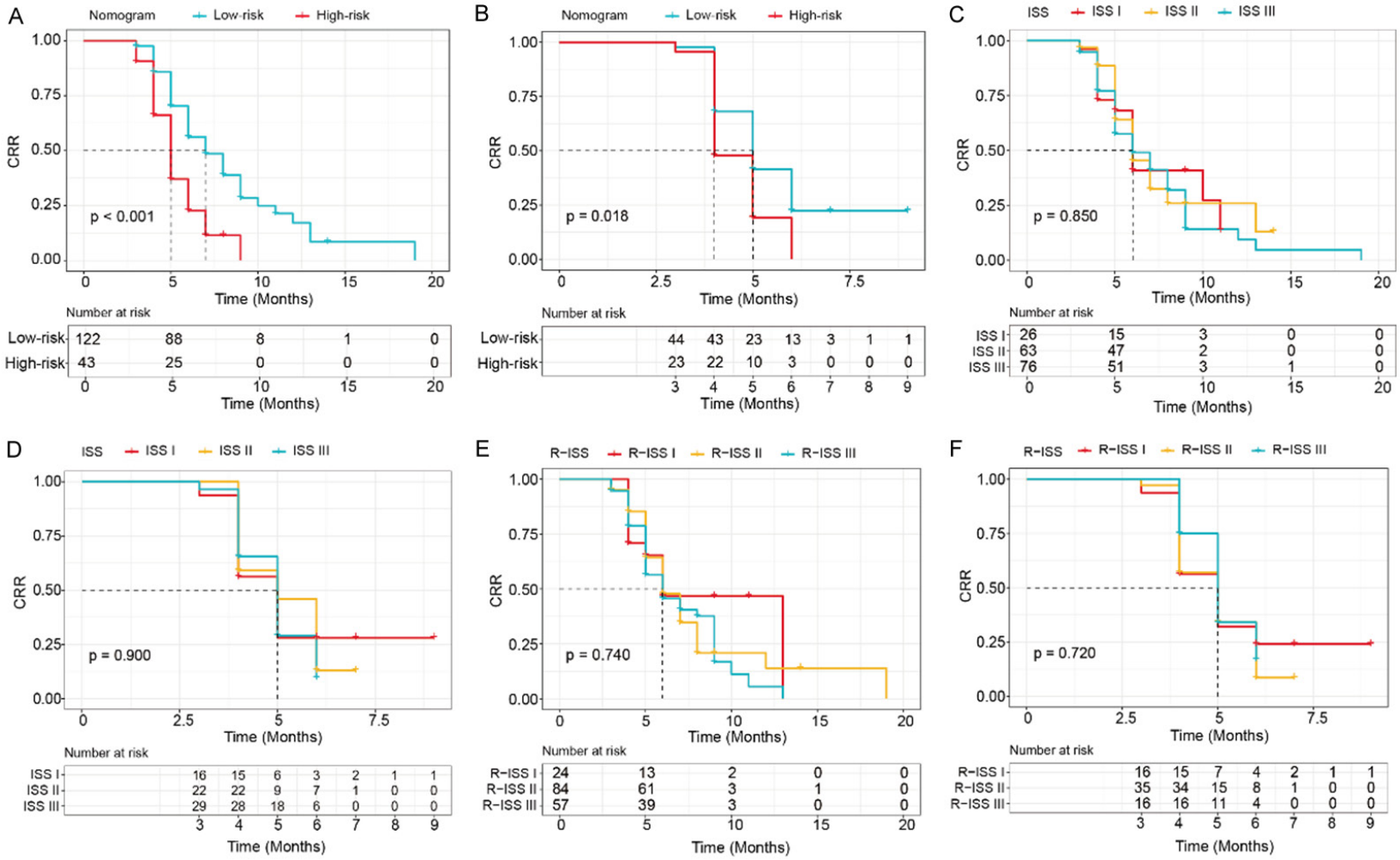
Figure 4. Establishment and validation of the Nomogram model. A, B. The ROC analysis of Nomogram predicted 4-, 5-, 6-month CR in the training and internal validation sets. C, D. The calibration plot of Nomogram at 6-month CR in the training and internal validation sets. E, F. The time-depend AUC of four models in the training and internal validation sets. G, H. The time-depend C-index of four models in the training and internal validation sets.

years, patients treated with bortezomib, and patients with abnormal FISH. The high-risk group included 38 patients (27.3%) under the age of 70 years old, compared to the low-risk group, their CR rate was significantly lower (P<0.001, **Figure 6A**). Patients treated with bortezomib and classified as low-risk had a higher CR rate than patients classified as high-risk (P<0.001, **Figure 6B**). The curves of patients with abnormal FISH divided by Nomogram also showed significant differences (P<0.001, **Figure 6C**). Therefore, the Nomogram stratification still applied to the three different subgroups.

These findings indicated that the stratification effect of alternative MM staging systems was not significant, particularly in patients with ISS III, R-ISS II, and R2-ISS III, and that these three patient groups required accurate stratification. Notably, the Kaplan-Meier curve analysis showed that patients with ISS III, R-ISS II, and R2-ISS III could be classified into a low-risk group by our Nomogram model, with favorable outcomes (P=0.001, P=0.002, P<0.001, **Figure 6D-F**).

Discussion

In our study, we retrospectively analyzed the basic clinical information and data of 232 patients with NDMM and constructed a new simple short-term prognostic model (Nomogram) integrating urinary IgG, CO_2CP, and TP, for predicting the probability of 4-, 5-, 6-month CR based on univariate- and multivariate Cox regression analysis. Compared to other MM staging systems, our Nomogram model's risk


A
Nomogram
Low-risk
High-risk
CRR
p < 0.001
Time (Months)
Number at risk
Low-risk 122 88 8 1 0
High-risk 43 25 0 0 0
B
Nomogram
Low-risk
High-risk
p = 0.018
Number at risk
Low-risk 44 43 23 13 3 1 1
High-risk 23 22 10 3 0 0 0
C
ISS
ISS I
ISS II
ISS III
p = 0.850
Number at risk
ISS I 26 15 3 0 0
ISS II 63 47 2 0 0
ISS III 76 51 3 1 0
D
ISS
ISS I
ISS II
ISS III
p = 0.900
Number at risk
ISS I 16 15 6 3 2 1 1
ISS II 22 22 9 7 1 0 0
ISS III 29 28 18 6 0 0 0
E
R-ISS
R-ISS I
R-ISS II
R-ISS III
p = 0.740
Number at risk
R-ISS I 24 13 2 0 0
R-ISS II 84 61 3 1 0
R-ISS III 57 39 3 0 0
F
R-ISS
R-ISS I
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p = 0.720
Number at risk
R-ISS I 16 15 7 4 2 1 1
R-ISS II 35 34 15 8 1 0 0
R-ISS III 16 16 11 4 0 0 0

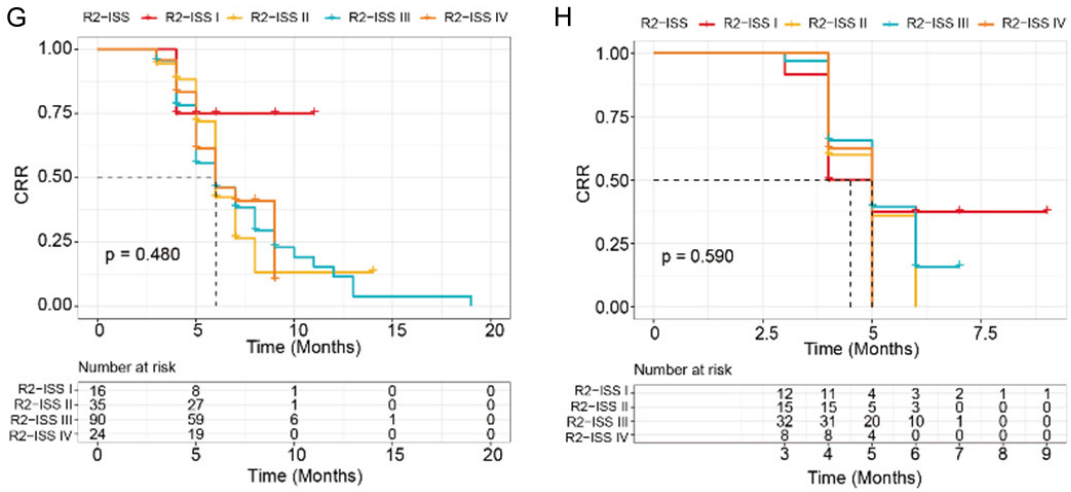

Figure 5. Kaplan-Meier curves stratified by four models in the training and internal validation sets. A, B. The stratification of Nomogram. C, D. The stratification of ISS. E, F. The stratification of R-ISS. G, H. The stratification of R2-ISS.

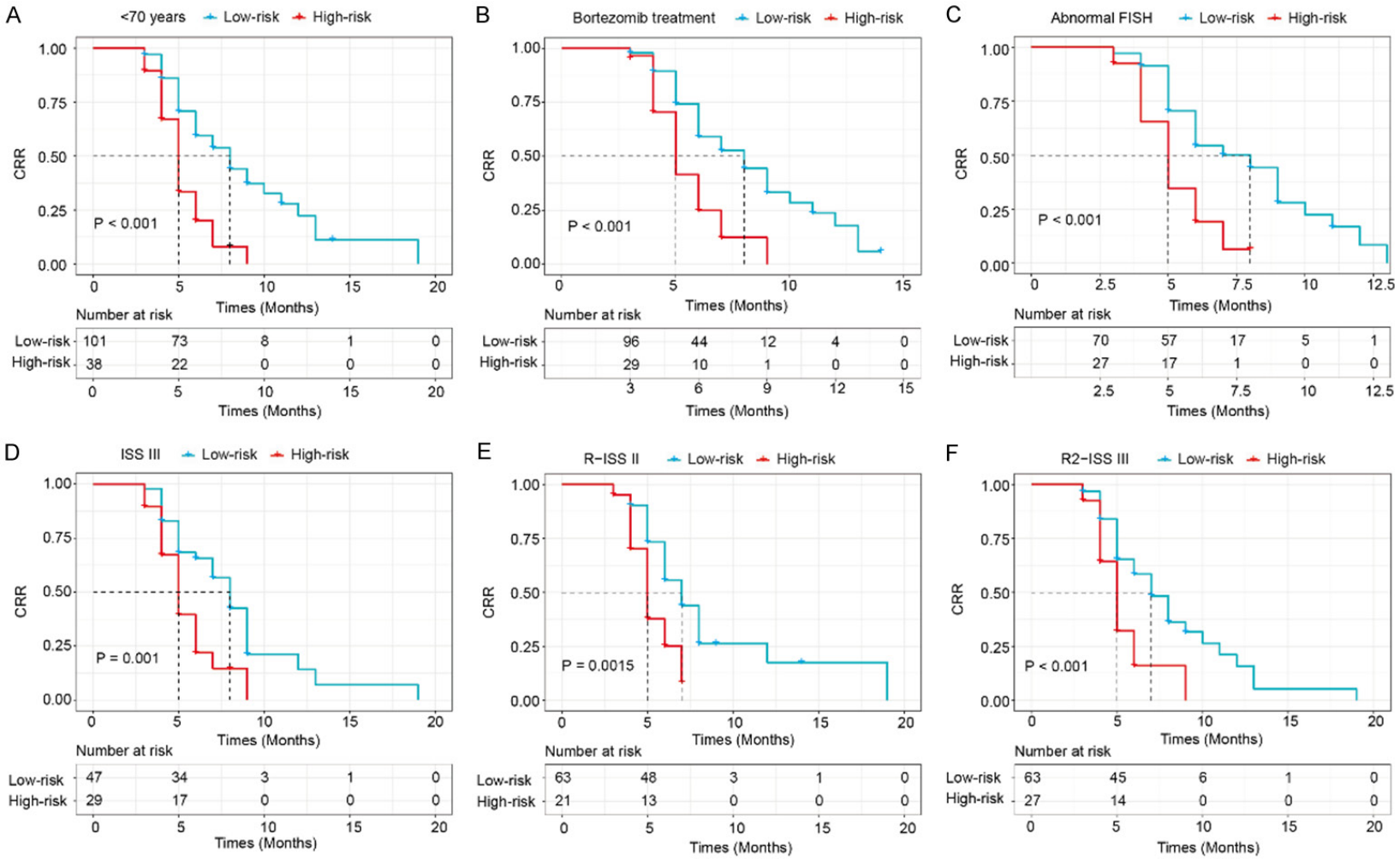

Figure 6. Kaplan-Meier curves of specific subgroups stratified by the Nomogram in the training set. A. Age <70 years old. B. Bortezomib therapy. C. Abnormal FISH. D. ISS III. E. R-ISS II. F. R2-ISS III.

stratification ability was validated in both the training and internal validation sets. This allowed for further identification of high-risk NDMM patients and prediction of their short-term remission.

Although the widely utilized MM staging systems mainly included ISS, R-ISS, and R2-ISS staging, which greatly promoted the risk stratification of MM patients, there were still shortcomings such as high economic cost of examination, unidentification of some high-risk patients and lack of external verification of big data. Thus, further studies were required to establish a more comprehensive and clinically practical prognostic stratification system for NDMM.

Inflammatory markers such as NLR, PLR, LMR, SIRI, and SII have all been extensively researched. Owing to the widespread use and convenience of routine blood testing, it was more difficult to eliminate these markers, which makes investigating their prognostic significance in tumors easier. According to a study, patients with low LMR, high PLR, and high NLR had a shorter survival rate than their counterparts [25]. In a study conducted by Zhang et al, they developed a predictive model for patients with primary extramedullary multiple myeloma and demonstrated that MLR≥0.32 was one of the prognostic factors [11]. Other studies also provided evidence that high NLR and SIRI were related to shorter OS in MM [2, 15]. Decreased RPR and elevated monocyte count were relative to poor prognosis in MM patients [26]. However, in contrast to the previous findings, our results from univariate Cox analysis revealed that NLR, PLR, LMR, SIRI, and SII were not independent short-term prognostic factors. The potential cause could be that, whereas the previous studies all examined the survival prognosis of MM patients, our study focused on the short-term prognosis; as a result, the clinical significance of inflammation indicators in short-term prognosis was not significant. In addition, Khosravi et al explored the clinical value of Calprotectin (CP) in MM and indicated that the fecal CP of NDMM patients was significantly higher than that of MM patients after treatment [27]. Therefore, this insinuates the need for investigation of the prognostic value of more inflammatory markers in MM.

Nutritional parameters have also been a subject of research interest in various tumors. Another popular topic was the nutritional parameters' prognostic study in different tumors. The prognosis influence of diffuse large B-cell lymphoma (DLBCL), peripheral T-cell lymphoma, and other leukemias can all be evaluated utilizing the CONUT score, which not only indicates the body's nutritional state but also the inflammatory response to blood tumors [28]. One study calculated CONUT scores in 64 patients with symptomatic MM and concluded that patients with low CONUT scores had better overall survival than those with high scores [9]. PNI was a preoperative evaluation index calculated by albumin and lymphocyte counts [21] and also resulted in further progress from MGUS to MM [12]. According to a meta-analysis and systematic review, patients with solid tumors had a lower survival rate when their HALP score was low [13]. Consistent with previous research, our investigation demonstrated that PNI<33.85 was a short-term prognostic characteristic in univariate Cox regression; however, it was ultimately excluded from the Nomogram. This could be because of the study's small sample size. Furthermore, the use of lipid-lowering drugs was associated with NDMM, but TC, TG, HDL-C, and LDL-C were not prognostic factors in this diagnosis.

Urinary IgG, TF, α1-MG, and β2-MG are examples of nephrotic indicators that reflect the state of glomerular filtration and renal tubule secretion function in the body. These indicators are always used to assess renal function in patients with diabetic nephropathy and chronic kidney disease [29, 30]. Recently, more studies on the clinical utility of these renal indicators in other diseases have emerged, Mravljak et al's study found that the ratio of urinary IgG to albumin can better reflect the therapeutic effect of ANCA-associated glomerulonephritis [31], and another one showed that urinary IgG may be a marker of atherosclerotic load [32]. Renal impairment was also one of the common complications in MM patients, which affected the clinical prognosis of MM patients [33]. Therefore, we examined the relationship between indicators of urinary nephropathy and the duration of short-term remission in MM patients. Urinary IgG≥7.93 mg/L was eventually determined to be a risk factor for the short-term

prognosis of NDMM and was included in the construction of the Nomogram.

In addition to urinary IgG, CO_2CP and TP were finally included in the establishment of the Nomogram in our study. Kaplan-Meier curve analysis also showed that MM patients with $CO_2CP<20.7$ mmol/L and TP≥123.4 g/L had a worse short-term prognosis. CO_2CP is an index that reflects the level of bicarbonate in plasma and evaluates acid-base metabolism. A study found that $CO_2CP<23$ mmol/L was an independent risk factor for hospital mortality in patients with acute kidney injury and can be used as an indicator of metabolic acidosis [34]. Low CO_2CP was found to be a risk factor for NDMM in our study. One potential mechanism for this is that metabolic acidosis develops when renal tubular function is severely compromised in micromineral (MM), leading to a drop in CO_2CP. Thus, additional research was required to elucidate the predictive significance of CO_2CP and the precise mechanism underlying the decline in CO_2CP in MM.

The total protein content (TP) in serum or plasma, which is composed of albumin and globulin, was determined to be a significant prognostic factor in multiple myeloma (MM) patients. The overall survival of these patients was found to be significantly lower when their TP was greater than 6.4 g/dL [35]. According to other research, TP in MM patients was significantly higher than in other nephrotic patients, and TP>68.45 g/L was associated with an increased risk of MM observed in patients visiting the nephrology department. Additionally, TP in MM patients was also significantly higher than in normal populations [36, 37]. Our findings were consistent with the earlier research, which supported the prognostic importance of TP in MM. It was also important to monitor the dynamic changes in TP that occurred during treatment. By combining urinary IgG with CO_2CP and TP, we were able to construct a short-term prognostic model in our study that outperformed other staging systems (ISS, R-ISS, and R2-ISS) in terms of discrimination (higher C-index) and clinical utility, as evidenced by the time-dependent C-index in the training and internal validation sets. These findings implied that our model might be helpful in individual short-term prognosis predictions and personalized treatment guidance. For instance, patients with high total scores tended to have a worse short-term response, so more frequent follow-up might be necessary for those patients to improve their prognosis.

However, our study has limitations. Firstly, the study's retrospective design, small sample size, single-center setup, lack of external data validation, and some findings inconsistent with earlier findings were its main limitations. Thus, future studies require an increased patient number to verify the reliability. In clinical settings, prognostic models need to demonstrate good performance in different patient population and medical scenarios. Multi-center external validation can provide evidence of the reliability and effectiveness of the model in practical clinical applications, thereby supporting clinical decision-making. Secondly, the prognostic model we developed lacked a long-term prognosis analysis and was primarily focused on the short-term prognosis of MM patients. Lastly, our study did not analyze some potential variables, such as CP, red cell distribution width-platelet ratio (RPR), and sociodemographic characteristics, due to a lack of relevant data. Thus, to construct a more reliable prognostic staging system in the future, the factors mentioned above should be included for comprehensive analysis.

Conclusion

In this study, we constructed a simple short-term prognostic Nomogram for NDMM based on urinary IgG, CO_2CP, and TP. Compared with the other three MM staging systems, the Nomogram had good differentiation and clinical net benefit. Convenient indicator detection techniques included in the Nomogram were anticipated to reduce treatment costs and make the concept more widely accepted, offering a fresh approach to MM clinical decision-making.

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Disclosure of conflict of interest

None.

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Table S1. The C index results of Nomogram, ISS stage, R-ISS stage, R2-ISS stage respectively in the training and internal validation sets

Model and stages	Training set			Internal validation set		
	C index	CI 95% CI	P	C index	CI 95% CI	P
Nomogram	0.691	0.661-0.721	/	0.581	0.524-0.638	/
ISS stage	0.516	0.480-0.552	P<0.001	0.491	0.436-0.546	P<0.001
R-ISS stage	0.511	0.475-0.547	P<0.001	0.544	0.492-0.596	P<0.001
R2-ISS stage	0.523	0.490-0.556	P<0.001	0.493	0.439-0.547	P<0.001

Table S2. Univariate Cox regression analysis of training set

Variables	β	SE	HR	95% CI	P
Sex (female vs. male)	0.353	0.206	1.424	0.951-2.131	0.086
Age (≥70 vs. <70)	0.232	0.263	1.261	0.752-2.113	0.379
Chemotherapy regimen (Non Bortezomib treatment vs. Bortezomib treatment)	0.435	0.220	1.545	1.003-2.378	0.048
del(13q) (positive vs. negative)	-0.304	0.224	0.738	0.476-1.144	0.174
del(17p) (positive vs. negative)	0.436	0.370	1.546	0.748-3.195	0.239
IGH rearrangement (positive vs. negative)	0.335	0.225	1.398	0.899-2.172	0.137
1q+ (positive vs. negative)	0.114	0.204	1.121	0.751-1.673	0.575
FISH (abnormal vs. normal)	0.065	0.213	1.067	0.702-1.621	0.761