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Original Article

Prognostic value of the Controlling Nutritional Status score in patients with newly diagnosed multiple myeloma

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Abstract: Objective: There is some evidence indicating that the Controlling Nutritional Status (CONUT) score is a prognostic factor in patients with hematological malignancies, including multiple myeloma (MM). The aim of this study was to assess the prognostic value of the CONUT score in newly diagnosed MM. Method: We retrospectively investigated multiple clinical variables, including the CONUT score, age, sex, body mass index, M protein type, International Staging System (ISS) stage, Durie-Salmon (DS) stage, and blood cell count, in 58 patients with newly diagnosed MM. Result: There was a significant correlation between a high CONUT score (>5.5) and poor OS. The prognostic impact of this score was more significant in patients with a low ISS or DS stage. In univariate analysis, the white blood cell count (P=0.021), monocyte count (P=0.022), eosinophil count (P=0.004), and lactic dehydrogenase (LDH) (P=0.042) predicted OS. Multivariate analysis identified the CONUT score (P=0.012), monocyte count (P=0.008), eosinophil count (P=0.031), and LDH (P=0.001) to be independent prognostic factors for overall survival (OS). Conclusion: The CONUT score is a useful prognostic indicator in patients with MM, especially those with a low ISS or DS stage. The monocyte count, eosinophil count, and LDH are independent prognostic factors in these patients.

Keywords: Multiple myeloma, CONUT score, prognosis, overall survival

Introduction

Multiple myeloma (MM) is a B-cell neoplasm derived from monoclonal gammopathy of undetermined significance, which develops into smoldering myeloma, and eventually into symptomatic myeloma [1]. MM is characterized by malignant proliferation of plasma cells in bone marrow, excessive monoclonal immunoglobulins, dysfunction in relevant organs, and complicated manifestations, including hypercalcemia, anemia, renal dysfunction, and osteolytic bone lesions [2, 3].

Development of newer drugs, including immunomodulatory drugs, proteasome inhibitors, and CD38-targeting antibodies, has prolonged survival time in patients with MM, but eventually most of them die of this disease [4]. In view of the significant heterogeneity in biological behavior and clinical manifestations of MM, accurate evaluation of the prognosis and risk stratification are essential to ensure appropriate treatment [5]. At present, the prognosis of patients with MM is determined using the International Staging System (ISS), revised ISS, Durie-Salmon (DS) Staging, Mayo Stratification of Myeloma And Risk-adapted Therapy (mSMART), and other indicators [6]. However, the current prognostic evaluation system does not attach importance to the role of nutritional status.

The Controlling Nutritional Status (CONUT) score is a nutritional index that consists of three indicators, namely, serum albumin, total cholesterol, and the absolute lymphocyte count [7]. This score has been found to have prognostic value in various solid malignancies, including colorectal cancer, small hepatocellular carcinoma, and gastric cancer [8]. Several reports have suggested that the CONUT score might

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Table 1. Values used to calculate the CONUT score

Parameters	Normal	Light	Moderate	Severe
ALB (g/L)	≥35.0	30.0-34.9	25.0-29.9	<25.0
Score	0	2	4	6
CHO (mg/dL)	≥180	140.0-179.9	100.0-139.9	<100.0
Score	0	1	2	3
ALC (10^9/L)	>1.6	1.2-1.6	0.8-1.2	<0.8
Score	0	1	2	3
COUNT score	0-1	2-4	5-8	8-12

ALB, serum albumin; ALC, absolute lymphocyte count; CHO, total cholesterol; CONUT, Controlling Nutritional Status.

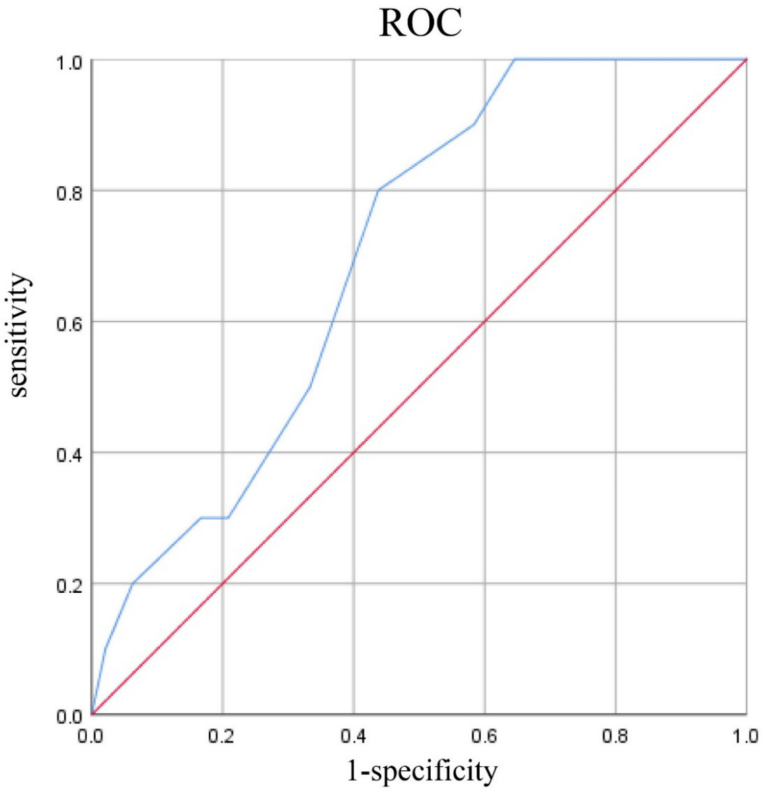

Figure 1. Receiver-operating characteristic curve showing the predictive value of the CONUT score. Notes: AUC, 0.701; 95% CI, 0.551-0.851; P=0.047. CONUT, Controlling Nutritional Status; AUC, area under curve; CI, confidence interval; ROC, receiver-operating characteristic.

also be a prognostic factor in patients with hematological malignancies, including MM [9-11]. Therefore, we performed this retrospective study to determine the prognostic value of the CONUT score in patients with MM.

Patients and methods

Patients

Patients diagnosed as having symptomatic MM based on the International Myeloma Working Group criteria at Hebei General Hospital in China between June 2016 and June 2022 were retrospectively enrolled. Inclusion criteria: (1) Meet the diagnostic criteria of *Guidelines for the Diagnosis and Mana-gement of Multiple Myeloma in China (2022 revision)* [5]; (2) Age ≥18 years; (3) Newly diagnosed MM patients. Exclusion criteria: (1) Incomplete initial clinical data; (2) Regular treatment with less than 4 courses of treatment; (3) Lost follow-up. The final follow-up date was December 2022. Two researchers collected data, and when disputes arose, the decision was made by the third researcher. The study protocol was approved by the ethics committee of Hebei General Hospital. The requirement for informed consent was waived in view of the retrospective nature of the research. Comprehensive clinical information was collected, including age, sex, body mass index, M protein type, ISS stage, Durie-Salmon stage, blood cell count, β2-microglobulin, serum C-reactive protein, erythrocyte sedimentation rate, serum albumin, total cholesterol, lactic dehydrogenase (LDH), serum calcium, and serum corrected calcium [5].

CONUT score

As a tool for controlling nutritional status, the CONUT score is calculated from serum albumin, total cholesterol, and the absolute lymphocyte count. The scoring criteria are shown in **Table 1**. The optimal cut-off CONUT score for overall survival (OS) was calculated to be 5.5 by receiver-operating characteristic curve analysis (**Figure 1**).

Statistical analysis

The optimum cut-off CONUT score was calculated by receiver-operating characteristic curve

Table 2. Demographic and clinical characteristics of 95 patients with multiple myeloma

Characteristic		N (%)
Gender	Male	29 (50%)
	Female	29 (50%)
Age (year)	≥65	31 (53.4%)
	<65	27 (46.6%)
BMI (Kg/m^2)	Obesity (≥30)	5 (8.6%)
	Non-obesity (<30)	53 (91.4%)
M protype type	IgG	23 (39.7%)
	IgA	15 (25.9%)
	IgD	4 (6.9%)
	Light chain	14 (24.1%)
	Non-secretory	1 (1.7%)
	Biclonal	1 (1.7%)
ISS	I	6 (10.3%)
	II	23 (39.7%)
	III	29 (50%)
DS	I	4 (6.9%)
	II	10 (17.2%)
	III	44 (75.9%)
Subgroup	A	36 (62.1%)
	B	22 (37.9%)
HGB (g/L)	>100	14 (24.1%)
	≤100	44 (75.9%)
ALB (g/L)	≥35	23 (39.7%)
	<35	35 (60.3%)
β2-MG (mg/L)	<3.5	15 (25.9%)
	≥3.5	43 (74.1%)
Serum calcium (mmol/L)	≤2.65	53 (91.4%)
	>2.65	5 (8.6%)

In accordance with the DS stage, A indicates a serum creatinine level <177 μmol/L and B indicates a serum creatinine level ≥177 μmol/L. ALB, serum albumin; β2-MG, β2-microglobulin; BMI, body mass index; DS, Durie-Salmon; HGB, hemoglobin; ISS, International Staging System.

analysis. Counting data was represented by frequency and proportion, and measurement data were represented by mean ± standard deviation. OS was calculated from the date of diagnosis of MM to the date of death from any cause or the last follow-up, whichever came first. The Kaplan-Meier method was used for survival analysis, and the log-rank test was used to examine the difference between the survival curves. Univariate and multivariate analyses were performed using a Cox proportional regression model. All statistical analyses were performed using SPSS software (version 26.0; IBM Corp., Armonk, NY, USA). A *P*-value <0.05 was considered statistically significant.

Results

Patient characteristics

Fifty-eight patients (29 men, 29 women) were diagnosed as having MM during the study period (**Table 2**). The median patient age was 65 years (range 36-88). Six patients had ISS stage I disease, 23 had stage II, and 29 had stage III. Four patients were DS stage I, 10 were stage II, and 44 were stage III. Thirty-six patients had DS subtype A and 22 had DS subtype B. The M protein types were IgG (n=23), IgA (n=15), IgD (n=4), light chain (n=14), biclonal gammopathy (n=1), and non-secretory (n=1). According to the optimal cut-off CONUT score on the receiver-operating characteristic curve (**Figure 1**), 29 patients had a low score (<5.5) and 29 patients had a high score (≥5.5). Median OS has not been reached.

Prognostic value of the CONUT score for OS

Kaplan-Meier survival analysis indicated that patients with a high CONUT score had a worse prognosis (P=0.038; **Figure 2**). We then performed a subgroup analysis based on ISS stage, DS stage, and age. OS in patients with ISS stage I or II disease had worse OS if their CONUT score was high (P=0.015; **Figure 3**). OS was significantly worse in patients with DS stage I or II disease and a high CONUT score (P=0.027; **Figure 3**). However, there was no significant difference in OS according to the patients' age.

Univariate and multivariate analyses for OS

Table 3 shows the results of the univariate and multivariate analyses for OS in patients with MM. In univariate analysis, the white blood cell count (hazard ratio [HR] 1.386, 95% confidence interval [CI] 1.051-1.829; P=0.021), monocyte count (HR 1.004, 95% CI 1.001-1.008; P=0.022), eosinophil count (HR 1.011, 95% CI 1.004-1.019; P=0.004), and LDH (HR 1.007, 95% CI 1.001-1.014; P=0.042) were identified

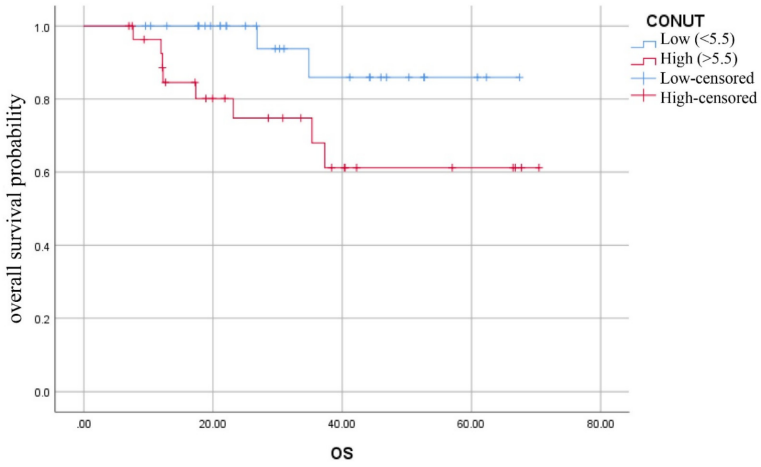

Figure 2. Kaplan-Meier curves showing overall survival in the study cohort. Notes: P=0.038. CONUT, Controlling Nutritional Status.

as having a significant prognostic impact in patients with MM.

The seven factors with a *P*-value <0.1 (white blood cell count, neutrophil count, monocyte count, eosinophil count, LDH, CONUT score, and corrected calcium level) were entered into multivariate analysis. The results showed that the monocyte count (HR 1.006, 95% CI 1.002-1.010; P=0.008), eosinophil count (HR 1.011, 95% CI 1.001-1.021; P=0.031), LDH (HR 1.02, 95% CI 1.008-1.032; P=0.001), and CONUT score (HR 1.087, 95% CI 1.013-1.585; P= 0.012) were independent prognostic factors in patients with MM (**Table 2**).

Then, we performed ROC curve analysis on the survival prognosis of MM patients based on factors screened from multiple factors (**Figure 4**). The cutoff value of the CONUT score was calculated using the ROC curve, as shown in **Figure 1**.

Discussion

The CONUT score is a cost-effective and convenient nutritional indicator that has been confirmed to be a prognostic factor in several types of cancer, including esophageal neoplasms [12], gastric cancer, and colorectal cancer [13-15]. It has also been found to predict the prognosis in patients with hematologic malignancies [16], including MM and diffuse large B-cell lymphoma [17, 18]. The findings of our present study indicate that the baseline CONUT score is a factor that influences the prognosis in patients with newly diagnosed MM, which is consistent with previous reports of the CONUT score being a prognostic factor in patients with MM [9-11, 19, 20]. With the exception of the research by Liang et al. [19], the previous studies demonstrated that a high CONUT score is an independent indicator of a worse prognosis in these patients.

In our cohort, the CONUT score, monocyte count, eosinophil count, and LDH were found to be independent prognostic factors. Li et al. [20] also identified the monocyte count to be an independent prognostic factor in patients with MM (HR 11.284, 95% CI 22.968-42.897; P<0.001). The absolute monocyte count in peripheral blood is thought to reflect the bone marrow microenvironment. A recent study retrospectively evaluated the prognostic significance of monocytes in 10,822 patients with newly diagnosed MM and confirmed that an abnormal monocyte count was associated with poor OS [21].

Wong et al. [22] were the first to confirm the role of eosinophils in the pathology of MM by demonstrating that eosinophils could stimulate the proliferation of malignant plasma cells to promote the biology of MM. Other studies [23, 24] found that eosinophils are involved in acceleration of the growth and progression of MM, which might be the mechanism via which eosinophils impact the prognosis in patients with MM.

In clinical practice, the LDH level is an important factor in the diagnosis, treatment, and prognosis of hematological malignancies, including non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and MM. LDH reportedly plays a critical role in the initiation and metabolism of a tumor and has been identified as a sensitive indicator of hypoxia, anaerobic glycolysis, and malignant transformation during cell metabolism [25-27]. There is also some research showing that a high LDH level is associated with increased tumor invasiveness, a high proliferation rate, and presence of a tumor mass [28].

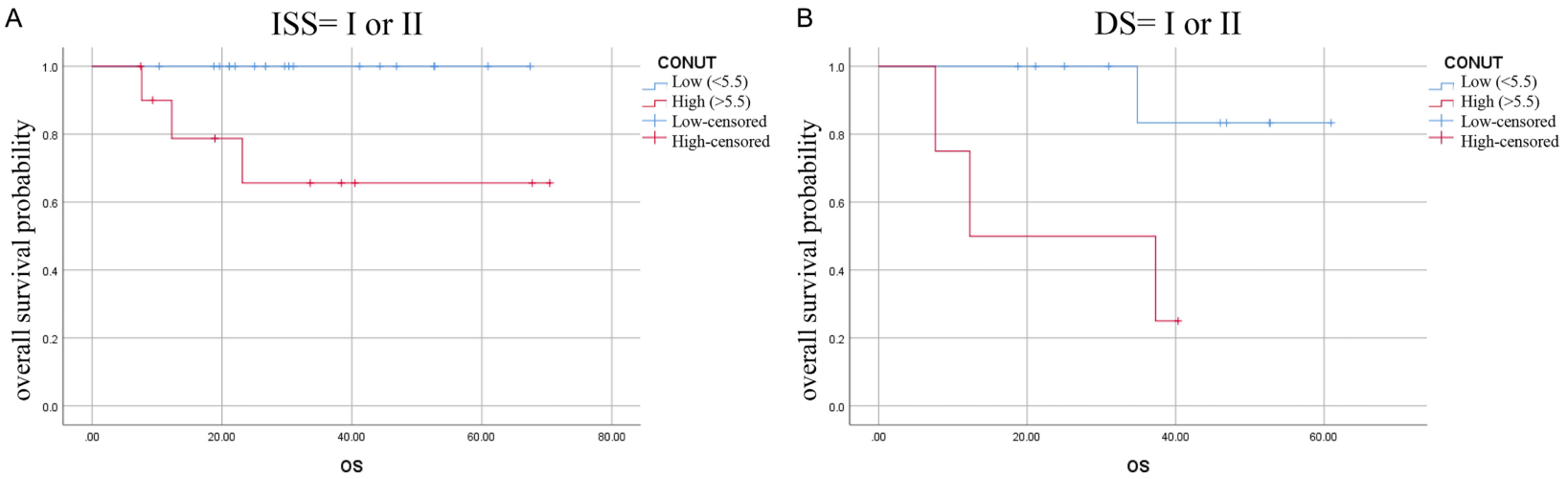

Figure 3. Kaplan-Meier curves showing overall survival according to disease stage. A. Estimated overall survival in patients with ISS stage I or II disease. B. Estimated overall survival in patients with DS stage I or II disease. Notes: A, P=0.015; B, P=0.027. DS, Durie-Salmon; ISS, International Staging System; CONUT, Controlling Nutritional Status.

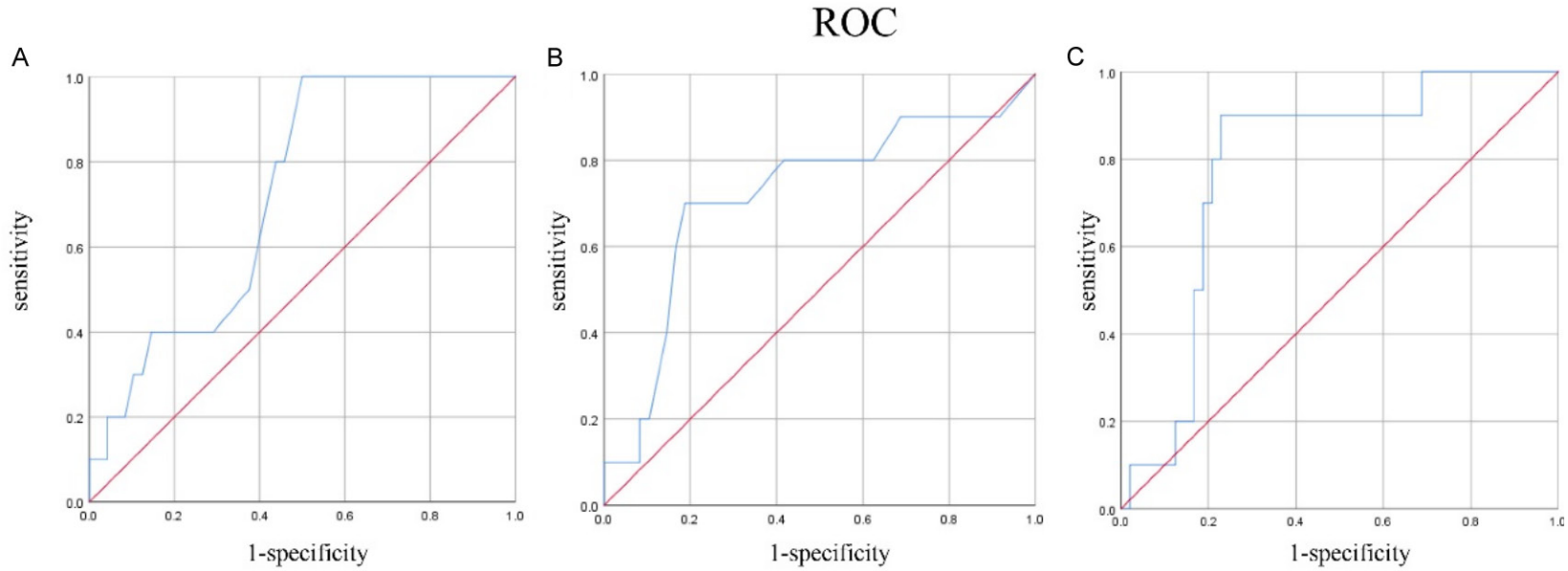

Figure 4. Receiver-operating characteristic curve. A. ROC curve analysis on the survival prognosis of MM patients based on MONO. AUC, 0.722; 95% CI, 0.577-0.867; P=0.028. B. ROC curve analysis on the survival prognosis of MM patients based on EO. AUC, 0.719; 95% CI, 0.527-0.911; P=0.031. C. ROC curve analysis on the survival prognosis of MM patients based on LDH. AUC, 0.785; 95% CI, 0.648-0.923; P=0.005. Notes: CONUT, Controlling Nutritional Status; MM, multiple myeloma; MONO, monocytes; AUC, area under curve; CI, confidence interval; EO, eosinophils; LDH, lactate dehydrogenase.

Table 3. Results from univariate and multivariate analyses of overall survival

Characteristic	HR	95% CI	P	HR	95% CI	P
Gender	2.637	0.681-10.21	0.16			
Age	1.037	0.983-1.094	0.189			
BMI	1.018	0.835-1.242	0.857			
M protein type	0.937	0.497-1.765	0.840			
Subgroup	0.66	0.35-1.244	0.199			
HGB	1.003	0.979-1.027	0.799			
RBC	1.04	0.528-2.048	0.91			
WBC	1.386	1.051-1.829	0.021			
PLT	1.001	0.995-1.007	0.742			
NEUT	1.356	0.996-1.845	0.053			
MONO	1.004	1.001-1.008	0.022	1.006	1.002-1.01	0.008
EO	1.011	1.004-1.019	0.004	1.011	1.001-1.021	0.031
BASO	1	0.988-1.012	0.995			
β2-MG	1.17	0.897-1.526	0.248			
ESR	1.007	0.992-1.023	0.35			
CRP	0.995	0.959-1.032	0.789			
LDH	1.007	1.001-1.014	0.042	1.02	1.008-1.032	0.001
Calcium	3.22	0.743-13.956	0.118			
CONUT	1.468	1.216-2.017	0.055	1.087	1.013-1.585	0.012
Corrected calcium	3.262	0.879-12.098	0.077			
ISS	0.646	0.328-1.271	0.206			
DS	1.283	0.68-2.42	0.442			
RDW	0.954	0.886-1.027	0.209			

ALB, serum albumin; β2-M, β2-microglobulin; BASO, basophils; BMI, body mass index; CHO, total cholesterol; CI, confidence interval; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; EO, eosinophils; ESR, erythrocyte sedimentation rate; HGB, hemoglobin; HR, hazard ratio; LDH, lactate dehydrogenase; MONO, monocytes; NEUT, neutrophils; PLT, platelets; RBC, red blood cells; RDW, red cell volume distributing width; WBC, white blood cells.

This research has some limitations, in particular its small sample size and short follow-up duration. Therefore, its participants may not be representative of the entire patient population with MM. Follow-up is being continued in these patients to determine the ability of the CONUT score to predict their prognosis.

In conclusion, this study found that the baseline CONUT score is a factor that independently influences the prognosis of patients with MM and that monocytes, eosinophils, and LDH are independent prognostic factors.

Disclosure of conflict of interest

None.

Abbreviations

ALB, serum albumin; β2-M, β2-microglobulin; BASO, basophils; BMI, body mass index; CHO, total cholesterol; CI, confidence interval; CONUT, Controlling Nutritional Status; CRP, C-reactive protein; DS, Durie-Salmon; EO, eosinophils; ESR, erythrocyte sedimentation rate; HGB, hemoglobin; HR, hazard ratio; ISS, International Staging System; LDH, lactate dehydrogenase; MM, multiple myeloma; MONO, monocytes; NEUT, neutrophils; OS, overall survival; PLT, platelets; RBC, red blood cells; RDW, red cell volume distributing width; ROC, receiver-operating characteristic; WBC, white blood cells.

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