

Changes in Laboratory Indexes for Multiple Myeloma Patients Before and After Autologous Stem Cell Transplant

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Purpose: Outcomes after autologous stem cell transplantation (ASCT) are quite variable and difficult to predict. Second-generation flow, second-generation sequencing, and other tests are invasive and expensive for patients. In this study, we aimed to analyze laboratory data before and after transplantation to look for laboratory indicators that could predict disease progression in patients with newly diagnosed multiple myeloma (NDMM) patients underwent ASCT.

Patients and Methods: Standard complete blood count (CBC) parameters, clinical biochemical, and immunological indicators on day -5 and day 90 after ASCT were obtained. Receiver-operating characteristic (ROC) curve was used to determine the cutoff values, we evaluated the predictive abilities of laboratory parameters for progression-free survival (PFS). Univariate and multivariate analyses were performed to evaluate the prognostic significance of variables associated with the PFS of 166 NDMM who underwent ASCT.

Results: At day-5, a low absolute monocyte count (AMC, $p=0.001$), systemic inflammation response index <1.56 (SIRI, $P=0.03$), serum calcium ($p=0.02$), and albumin ($p=0.006$) can predict for superior PFS. At Day +90, a high absolute neutrophil count (ANC, $p=0.008$) and lymphocyte-to-monocyte ratio (LMR, $p=0.02$), a low neutrophil-to-lymphocyte ratio (NLR, $p=0.02$) and SIRI <0.41 ($p=0.02$) predicted for superior PFS.

Conclusion: There are inflammation-related indicators derived from peripheral blood cell count (WBCC) – ANC, NLR, SIRI, and LMR - which can serve as potential biomarkers for predicting PFS of NDMM patients underwent ASCT.

Keywords: multiple myeloma, autologous stem cell transplantation, SIRI, lymphocyte-to-monocyte ratio

Introduction

The incurable malignancy of multiple myeloma (MM) is characterized by the abnormal proliferation of clonal plasma cells. It ranks as the second most prevalent malignant neoplasm in the hematopoietic system in numerous nations.^{1,2} Findings from prospective controlled trials comparing induction therapy with thalidomide and lenalidomide, followed by sequential ASCT and continuous novel drugs, have demonstrated that MM patients who undergo ASCT experience improved PFS, underscoring the significance of ASCT in the management of newly diagnosed MM.^{3,4} Nevertheless, the outcomes following ASCT exhibit considerable variability among patients. The progression of disease in multiple myeloma is characterized by variability and heterogeneity, as some patients may experience prolonged periods of remission while others may undergo rapid disease progression.⁵ A study suggested that the cumulative incidence rates of relapse at 1, 3, and 5 years in the short-term survival group were 9%, 63%, and 82%, respectively, compared to 2%, 20%, and 40%, in the long-term survivor group.⁶ The timing for assessing treatment response following transplantation lacks standardization and varies across different clinical trials. Following ASCT, patients with multiple myeloma have their tumor burden reevaluated approximately 100 days before initiating maintenance therapy.⁷ One of the reasons for recurrence was that multiple myeloma cell lines became resistant to proteasome inhibitors. There are several common mechanisms of resistance, such as mutations and aberrant expression of proteasome subunits, endoplasmic reticulum

stress, autophagy inhibition, activation of efflux drug pumps, bone marrow microenvironment, excessive nuclear export of proteins, and metabolic adaptation.⁸

The immunological microenvironment is correlated with clinical outcomes in multiple myeloma patients. In addition, recent studies have demonstrated that the LMR can provide useful insight into the immune status of the organism and can be a critical factor in predicting the prognosis of a variety of blood tumors and solid tumors. Meta-analysis of 13 studies on MM reported that the indexes NLR and LMR/MLR derived from WBC were useful biomarkers to predict prognosis.⁹ The LMR is calculated as lymphocyte count/monocyte count, and the NLR is calculated as neutrophil count/lymphocyte count. Multiple myeloma is characterized by anemia, leukopenia, and leukopenia thrombocytopenia, which is less common. Among the prognostic markers used in the Durie-Salmon staging system 2, anemia is associated with a worse prognosis.¹⁰ Several previous studies have demonstrated clinical significance for MM patients' prognosis according to red cell distribution (RDW), hemoglobin (Hgb), and platelet counts (PLT).^{11–13}

In a single-center retrospective study, we analyzed laboratory data for patients before and after autologous stem cell transplantation to identify indicators of disease progression. Our study examined the value and significance of these indicators in clinical treatment.

Materials and Methods

Patients

MM patients who underwent ASCT for the first time between January 2017 and March 2022 were included in our retrospective study. We received approval for the protocol of this study from Beijing Chao-Yang Hospital Ethics Committee (2022-ke-48) and institutional review board. Informed consent was waived by the Research Ethics Board of Beijing Chaoyang Hospital due to the retrospective nature of the study. Patient data was anonymized before analysis. All methods were carried out in accordance with the Declaration of Helsinki. A symptomatic diagnosis of MM as defined by the International Myeloma Working Group was required for eligibility. Patients who were younger than 18 years of age, who had undergone tandem ASCT, or who had undergone an allogeneic or ASCT before the trial were excluded.

Laboratory Measures

Baseline demographic data, disease and treatment characteristics, and Standard CBC parameters were collected at day 5 and day 90 post-ASCT,¹⁴ including Hgb, PLT, and MCV, as well as immune status markers called LMR and NLR. The blood routine analysis was performed using an automatic hematology analyzer (XN-20, Sysmex). Clinical biochemical and immunological indicators such as albumin, lactate dehydrogenase (LDH), creatinine, blood calcium, and Beta 2-microglobulin (β 2-mg) were also assessed. Biochemical Index Biochemical examination was carried out by an automatic biochemical analyzer (ADVIA2400, Siemens). SIRI is the neutrophil count multiplied by the monocyte count divided by the lymphocyte count. To evaluate the predictive powers and optimal cutoff values of other laboratory indicators of PFS, ROC curves and area under the ROC curves (AUCs) were used.

Statistical Analysis

Before running each statistical test, we checked whether its assumptions were met. We analyzed data using SPSS 22.0 (IBM Corp., Armonk, NY, USA) and R (version 3.5.3). Overall survival (OS) was defined as the time from ASCT to death, progression, or last follow-up date, while PFS was defined as the time from ASCT to death, progression, or last follow-up date. To compare OS and PFS, Kaplan-Meier (KM) curve estimates were applied, along with Log rank tests (Univariate analysis). An evaluation of the effect of these parameters on PFS was then conducted using multivariate Cox's proportional hazards model. The relationship between these parameters and PFS was then evaluated using Cox's proportional hazards model. P values < 0.05 were considered significant. The accuracy of our model was further verified by bootstrap validation using computer resampling for 1000 repetitions of simple random sampling with replacement. The calibration curve was employed to detect the concentricity between the model probability curve and the ideal curve (see [Supplementary Figures 1–3](#)).

Results

Patient Characteristics

In the final analysis, 166 patients underwent their first ASCT between 2017 and 2022. The baseline characteristics are presented in Table 1. The flow chart of inclusion and exclusion criteria is summarized in Figure 1. The median diagnosis age was 54.8 (50–60). IgA (n=36, 22%) and IgG (n=67, 40.9%) subtypes were found in most patients, as well as stage 3 myeloma (n = 56, 35.7%). FISH abnormalities most commonly found were 1q21 amplification (n=62, 37.1%) and t (11;14) (n=28, 16.8%). Lenalidomide, bortezomib, and dexamethasone (VRD, n=74, 47.2%) was the most commonly used induction regimen. Cyclophosphamide is the most commonly used mobilization scheme. There was one patient who died during the study, and the median follow-up time was 25 months (range: 3–67 months). Median PFS and OS were not reached. In the 3 years, 71% of respondents reported PFS. An analysis of the correlation between laboratory data in MM patients before and after ASCT was conducted in the entire series. There was a positive correlation between SIRI and AMC and a negative correlation between SIRI and LMR in Figure 2. ALB and serum were positively correlated ($r=0.59$, $p < 0.001$)

Differences in Pre-and Post-ASCT of Laboratory Tests

The lower, median, and upper quartiles for Neutrophil, lymphocytes, NLR, monocytes, HGB, PLT, MCV, LMR, ALB, LDH, Creatinine, Blood calcium, and β 2-MG on Day –5 and Day +90 are shown in Table 2. We first analyzed differences in pre-and post-ASCT median values and found that the ANC levels (2.6 versus $2.5 \times 10^3/\mu\text{L}$, $p = 0.84$) and Creatinine (58.9 versus $57.2 \mu\text{mol/L}$, $p = 0.16$) were similar. We also found that ALC levels (0.9 versus $1.8 \times 10^3/\mu\text{L}$, $p < 0.0001$), AMC (0.34 versus $0.35 \times$

Table 1 Baseline Characteristics of All Patients

Variable	Overall Study
	N=166
Age (years), median, (IQR)	54.8 (50–60)
Male (n, %)	85 (50.9)
ISS, n (%)	
1	48 (30.6)
2	53 (33.8)
3	56 (35.7)
Protein subtype, n (%)	
A	36 (22)
G	67 (40.9)
D	10 (6.1)
FIC	48 (29.2)
Non-secretory	3 (1.8)
Fish, n (%)	
1q21 amplification	62 (37.1)
TP53 mutation	10 (5.9)
t(14;16)	3 (1.8)
t(4;14)	25 (15.0)
t(11;14)	28 (16.8)
Missing	39
Induction, n (%)	
VRD	74 (47.25)
VCD	37 (24.73)
Mobilization, n (%)	
Cyclophosphamide	84 (46.15)
Etoposide	17 (9.3)

Abbreviations: IQR, interquartile range; ISS, International Staging System; VRD, bortezomib plus lenalidomide plus dexamethasone; VCD, bortezomib plus cyclophosphamide plus dexamethasone.

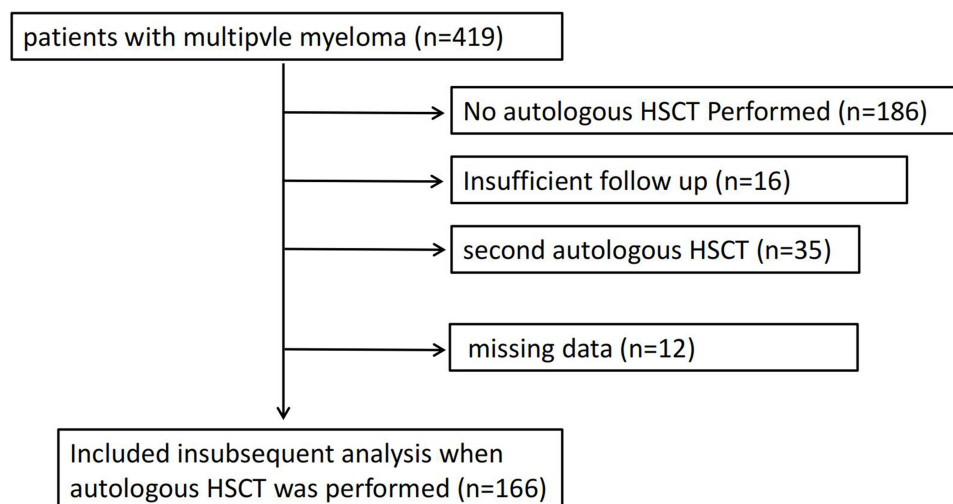


Figure 1 Flowchart depicting the composition of patients with MM who underwent ASCT in the study group.

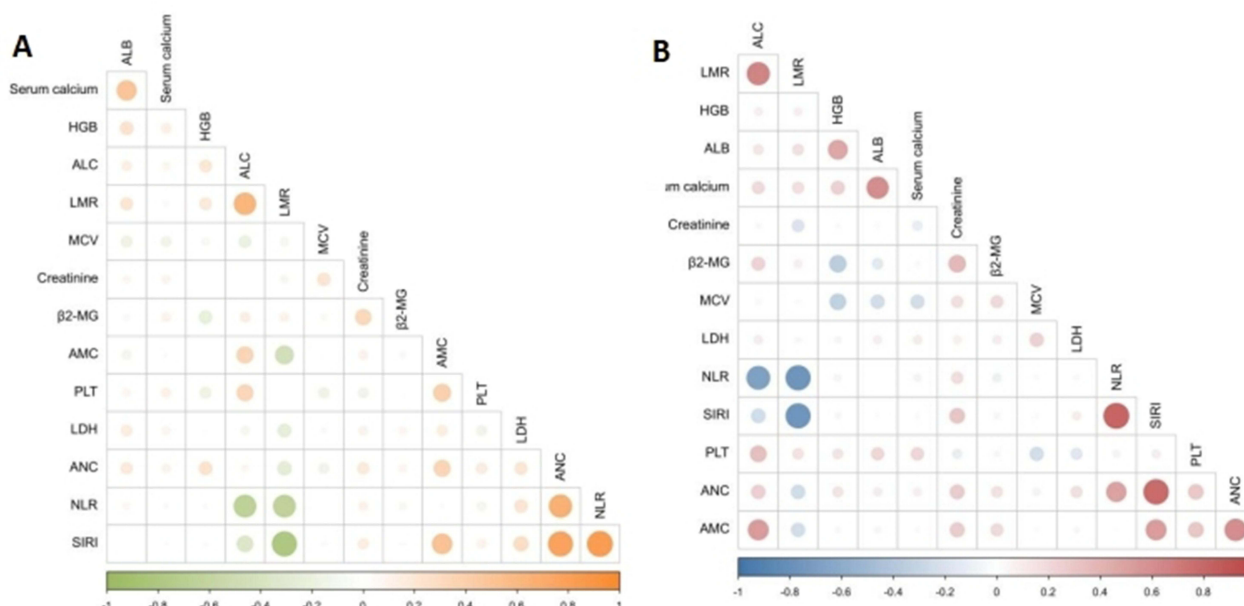


Figure 2 The association between laboratory data in MM patients before (A) and after ASCT (B).

$10^3/\mu\text{L}$, $p < 0.05$), LMR (2.5 versus $4.9 \times 10^3/\mu\text{L}$, $p < 0.0001$), HGB levels (121 versus 123 g/L, $p < 0.002$), MCV (92.2 versus 93 fL, $p < 0.003$), ALB (40.4 versus 44.5 g/L, $p < 0.0001$), β_2 -MG (2.2 versus 2.4 mg/L, $p < 0.0001$), LDH (176 versus 195 U/L, $p < 0.0001$), and serum calcium (2.2 versus 2.3 mmol/L, $p < 0.0001$) were increased. In comparison, NLR (3.0 versus $1.6 \times 10^3/\mu\text{L}$, $p < 0.0001$), PLT levels (199 versus $152 \times 10^3/\mu\text{L}$, $p < 0.0001$), and SIRI (1.04 versus 0.53 , $p < 0.0001$) were decreased after transplant. The results are shown in Figure 3.

Predictive Impact of Pre-and Post-ASCT Laboratory Tests

We then analyzed the impact of both pre-and post-ASCT ANC, ALC, AMC, NLR, ALB, LDH, and Blood calcium on PFS. First, we found that neither pre- nor post-ASCT ALC, ALB, LDH, or serum calcium predicted PFS. In addition, the day -5 ANC ($p = 0.9$), ALC ($p = 0.9$), NLR ($p = 0.9$), and LDH ($p = 0.2$), did not predict PFS. But a low AMC ($p = 0.0014$; Figure 4A), albumin ($p = 0.0055$; Figure 4B), serum calcium ($p = 0.02$; Figure 4C), and $\text{SIRI} < 1.56$ ($P = 0.03$; Figure 4D) can be predicted for superior PFS. At Day 90 post-ASCT, a high ANC ($p = 0.0078$;

Table 2 Median, Upper (75%), and Lower (25%) Quartiles for Neutrophil, Lymphocytes, NLR, Monocytes, HGB, PLT, MCV, LMR, ALB, LDH, Creatinine, Blood Calcium, and β 2-MG on Day -5 and Day +90

		Lower 25th Percentile	Median	Upper 25th Percentile
ANC, $10^3/\mu\text{L}$	D-5	1.9	2.6	3.5
	D+90	2.0	2.5	3.4
ALC, $10^3/\mu\text{L}$	D-5	0.6	0.9	1.1
	D+90	1.3	1.8	2.5
NLR, $10^3/\mu\text{L}$	D-5	2.0	3.0	4.2
	D+90	1.0	1.6	2.0
AMC, $10^3/\mu\text{L}$	D-5	0.25	0.34	0.47
	D+90	0.28	0.35	0.47
LMR, $10^3/\mu\text{L}$	D-5	1.7	2.5	3.2
	D+90	3.9	4.9	6.2
HGB, g/L	D-5	111	121	129
	D+90	113	123	123
PLT, $10^3/\mu\text{L}$	D-5	169	199	243
	D+90	123	152	197
MCV, fL	D-5	89.0	92.2	94.9
	D+90	89.8	93.0	96.7
ALB, g/L	D-5	38.8	40.4	42.8
	D+90	41.6	44.5	46.5
LDH, U/L	D-5	159	176	194
	D+90	175	195	221
Cr, $\mu\text{mol/L}$	D-5	49.2	58.7	70.1
	D+90	48.3	57.3	70.7
Blood calcium, mmol/L	D-5	2.1	2.2	2.3
	D+90	2.2	2.3	2.4
β 2-MG, mg/L	D-5	1.9	2.2	2.7
	D+90	2.1	2.4	3.2

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; Hgb, hemoglobin; PLT, platelet; WBC, white blood cell; MCV, mean corpuscular volume; LDH, lactate dehydrogenase; ALB, albumin; Cr, Creatinine; β 2-MG, β 2-microglobulin.

Figure 4E) and LMR ($p=0.02$; Figure 4F), a low NLR ($p=0.016$; Figure 4G) and SIRI <0.41 ($P=0.02$; Figure 4H) can be predicted for superior PFS, while the AMC and ALC had no impact on PFS. Accordingly, FISH results were used to categorize patients by high-risk and low-risk and examined their relationship with PFS (Figure 5).

Univariable and Multivariable Analysis for PFS Before or After ASCT

In our univariate and multivariate analyses, Cox's proportional hazards model was used to investigate the influence of other prognostic factors on PFS (Tables 3 and 4). A comprehensive analysis of the entire cohort indicated that patient PFS was significantly related to their ISS stage, NLR, and LMR after ASCT ($p=0.001$, $p<0.0001$, $p=0.004$). These and other potential confounding factors were included in a multivariate analysis, which yielded the following findings: the ISS stage and NLR were independently associated with superior PFS (hazard ratio (HR) 2.52, 95% CI 1.32–4.78, $p=0.005$; HR 3.93, 95% CI 2.18–7.09, $p<0.0001$). We have also developed a nomogram and further performed internal validation and calibration curves, as detailed in the [Supplementary Materials](#).

Discussion

It is currently the second most common hematological malignant tumor after leukemia. Multiple myeloma (MM) is a malignancy of plasma cells. MM patients newly diagnosed with the disease can benefit from the combination of proteasome inhibitors and/or immunomodulatory drugs combined with ASCT.¹⁵ MM prognosis remains difficult to

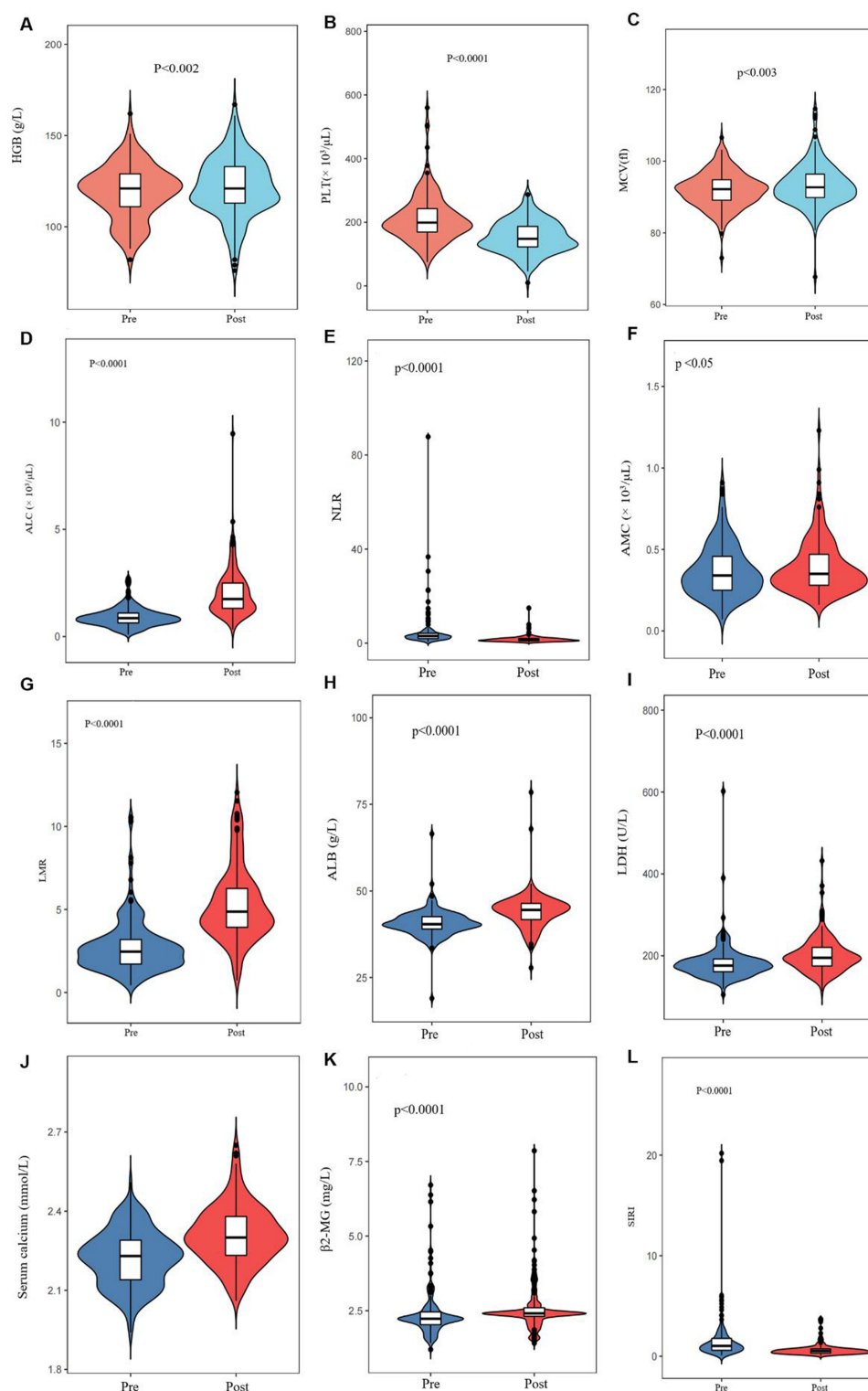


Figure 3 HGB levels (121 versus 123 g/L, $p < 0.002$, (A), MCV (92.2 versus 93 fL, $p < 0.003$, (C), ALC levels (0.9 versus $1.8 \times 10^3/\mu\text{L}$, $p < 0.0001$, (D), AMC (0.34 versus $0.35 \times 10^3/\mu\text{L}$, $p < 0.05$, (F), LMR (2.5 versus $4.9 \times 10^3/\mu\text{L}$, $p < 0.0001$, (G), ALB (40.4 versus 44.5 g/L, $p < 0.0001$, (H), LDH (176 versus 195 U/L, $p < 0.0001$, (I), serum calcium (2.2 versus 2.3 mmol/L, $p < 0.0001$, (J), and $\beta 2\text{-MG}$ (2.2 versus 2.4 mg/L, $p < 0.0001$, (K) were increased. In comparison, PLT levels (199 versus $152 \times 10^3/\mu\text{L}$, $p < 0.0001$, (B) NLR (3.0 versus $1.6 \times 10^3/\mu\text{L}$, $p < 0.0001$, (E)), and SIRI (1.04 versus 0.53, $p < 0.0001$, (L) were decreased after transplant.

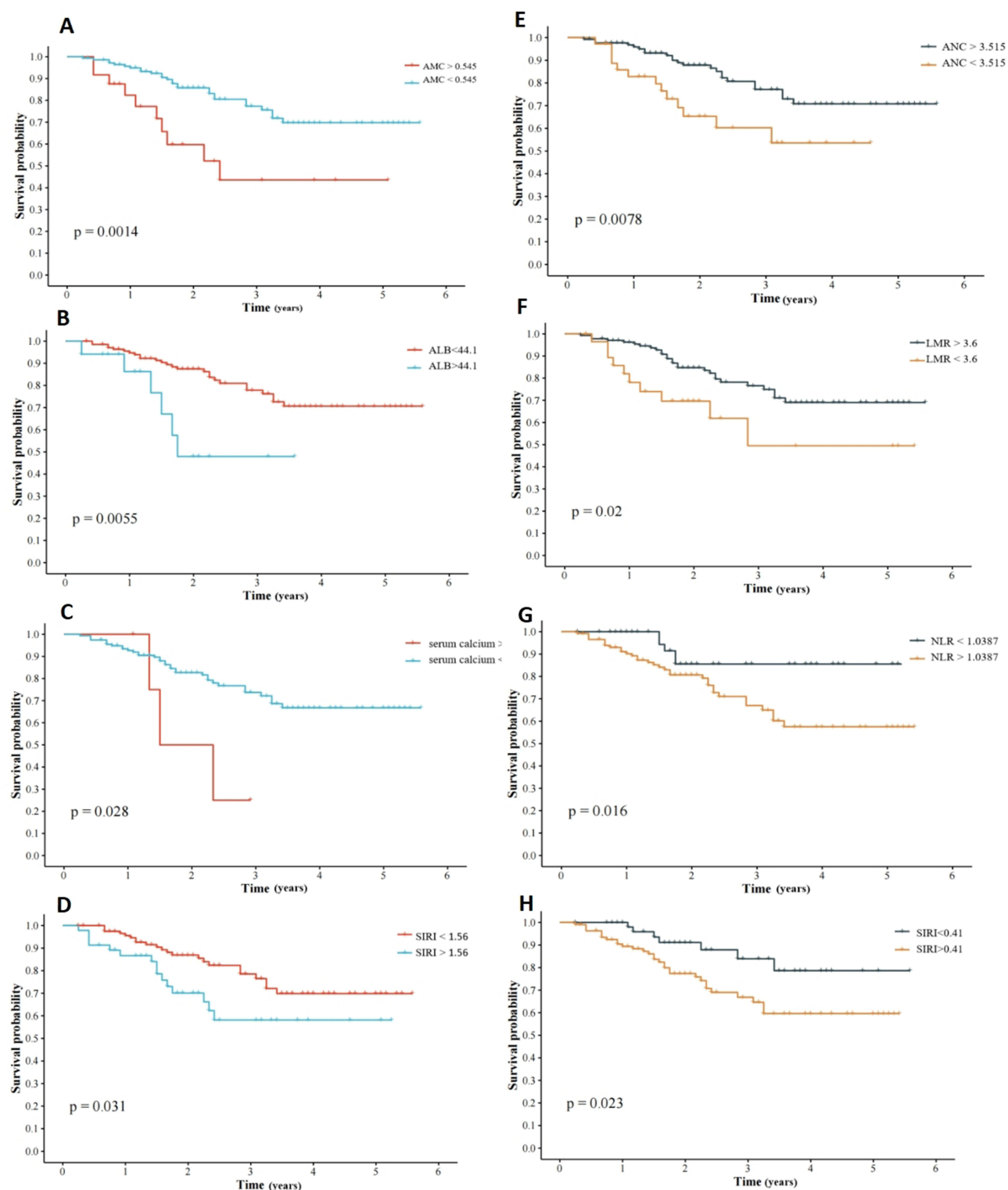


Figure 4 Progression-free survival based on the AMC (A), ALB (B), serum calcium (C), and SIRI (D) at Day 5 before-ASCT; Progression-free survival based on the ANC (E), NLR (F), LMR (G) and SIRI (H) at Day 90 post-ASCT.

predict, especially in post-ASCT settings because of considerable variability in survival rates. While existing diagnostic tools, such as the revised International Staging System (R-ISS), incorporate tumor cytogenetics and tumor load as factors, they cannot provide specific prognostic predictions post-ASCT. Further, alternative methods to predict disease progression after ASCT, such as minimal residual disease assessment (MRD) and positron emission tomography (PET), are both

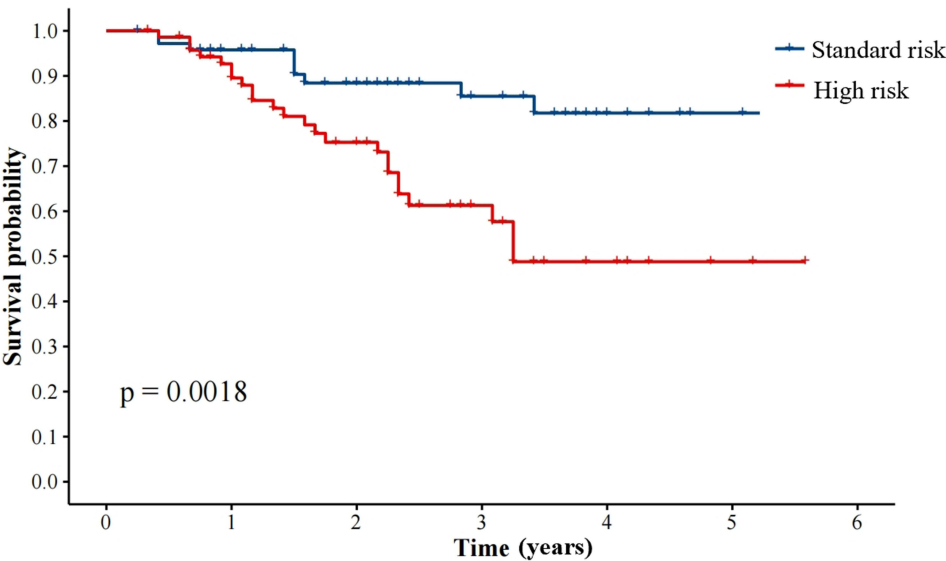


Figure 5 Comparison of PFS in patients with ASCT among standard risk and high risk.

expensive and time-consuming.^{16–18} Here, we analyzed laboratory data from patients before and after transplantation. Our study was to find laboratory indicators that predict progression after ASCT for NDMM patients.

Even though ASCT is the standard treatment for NDMM patients, ASCT is not curative, and progressions and relapses are common even if CR is attained after transplant.¹⁹

There were complex reasons for their relapse. Studies by the International Myeloma Working Group have shown that disease stage, poor response to chemotherapy, and lack of maintenance therapy after transplantation are associated with relapse. Of course, one possible factor is related to resistance to bortezomib, a commonly used proteasome inhibitor in the treatment of MM.²⁰ The mechanism of bortezomib is inhibition of the intracellular protein degradation pathway alters the levels of several intracellular regulatory and signaling proteins, effectively altering downstream cellular processes in a manner that leads to apoptosis or growth arrest.²¹ Bortezomib also has been reported to have some potential side effects that involve several systems, including the gastrointestinal, hematological, nervous, and musculoskeletal systems.²² Due to proteasome inhibitors are currently used to treat MM, most MM patients demonstrate drug-resistant relapse following long-term treatment. Consequently, the development of new therapeutic strategies, such as combination therapies, that overcome bortezomib

Table 3 Univariable and Multivariable Analysis for PFS Before ASCT

Variable	Univariable Analysis	P value	Variable	Multivariable Analysis	P value
	HR (95% CI)			HR (95% CI)	
Gender	1.11 (0.57–2.16)	0.75	AMC	5.53 (0.62–49.77)	0.13
Age	0.99 (0.94–1.04)	0.66	LMR	0.94 (0.71–1.24)	0.64
ANC	1.01 (0.82–1.24)	0.93	SIRI	0.39 (0.17–0.9)	0.02
ALC	0.67 (0.29–1.57)	0.36	Serum calcium	0.07 (0–12.53)	0.32
NLR	1.0 (0.97–1.04)	0.97			
AMC	10.36 (1.35–79.23)	0.02			
LMR	0.84 (0.65–1.09)	0.2			
SIRI	0.42 (0.18–0.94)	0.04			
ALB	1.0 (0.98–1.02)	0.68			
LDH	1.00 (1.0–1.01)	0.13			
Serum calcium	0.25 (0.01–7.24)	0.42			

Abbreviations: HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SIRI, neutrophil count multiplied by monocyte count divided by lymphocyte count; LDH, lactate dehydrogenase; ALB, albumin.

Table 4 Univariable and Multivariable Analysis for PFS After ASCT

Variable	Univariable Analysis	P value	Variable	Multivariable Analysis	P value
	HR (95% CI)			HR (95% CI)	
ISS	2.22 (1.38–3.59)	0.001	ISS	2.52 (1.32–4.79)	0.005
ANC	1.32 (1.0–1.75)	0.05	ANC	0.62 (0.38–0.99)	0.04
ALC	0.93 (0.63–1.38)	0.72	NLR	3.93 (2.18–7.09)	<0.0001
NLR	1.35 (1.18–1.54)	<0.0001	LMR	1.41 (1.0–2.0)	0.02
AMC	5.94 (1.1–32.75)	0.04			
LMR	0.72 (0.58–0.9)	0.004			
SIRI	0.72 (0.36–1.45)	0.35			
Albumin	0.98 (0.91–1.06)	0.61			
LDH	1.0 (0.99–1.01)	0.63			

Abbreviations: HR, hazard ratio; CI, confidence interval; ISS, International Staging System; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SIRI, neutrophil count multiplied by monocyte count divided by lymphocyte count; LDH, lactate dehydrogenase; ALB, albumin.

resistance is urgently needed. A study suggested that treatment with bortezomib and hydroxychloroquine prevents the pro-angiogenic effect of bortezomib, the proliferation of a small residual tumor PC clone, and thus the relapse.⁸

A myeloma microenvironment can enhance myeloma cell growth and survival and contribute to drug resistance.²³ A study of the tumor microenvironment revealed that inflammation plays a critical role in tumor occurrence, growth, and development.²⁴ Previous studies have suggested that SIRIs like NLR and MLR contribute to tumorigenesis, development, and prognosis.²⁵ Inflammatory markers have been shown to predict the outcome of different cancers, including non-small cell lung cancer, cervical cancer, and NDMM.^{26,27} The inflammatory microenvironment is closely linked to inflammatory cells.²⁸ There has been an increase in attention to systemic inflammatory markers in MM in recent years (NLR, PLR, and LMR/MLR). The LMR is indicative of the equilibrium between host immunity and the tumor environment. Various studies have demonstrated the significance of LMR in predicting patient outcomes at different stages, including diagnosis, and early treatment.^{29,30} In previous studies, NLR was an independent prognosticator for gastric cancer and other diseases.³¹ There is a meta-analysis showing that elevated NLR and decreased LMR predict poor OS/PFS in patients with NDMM. Immune responses are mediated by lymphocytes, a cellular component of the body. Patients with low lymphocyte counts have a suppressed immune system, which can negatively impact their prognosis for various types of cancer.²⁵ According to recent studies, LMR plays a critical role in MM survival. A significant difference in PFS and OS was observed between NDMM patients treated with bortezomib between the low and high LMR groups.^{32,33} In our study, we also found that these inflammatory markers can predict the prognosis of multiple myeloma after ASCT.

This study has potential limitations. The study included a limited number of patients. Although good internal verification results were obtained, the present study could not be externally verified due to the small number of cases. Second, this was a retrospective study that was conducted at a single center, so its representativeness may be limited. In our study, the longest follow-up period was 63 months, and obtaining long-term stable prediction results may require a longer follow-up period. In the future, we should conduct a multicenter investigation with a larger number of patients to validate our findings and explore the relationship between relapse mechanisms and drugs.

Conclusion

In conclusion, our results suggest that ANC, NLR, SIRI, and LMR are a series of inflammation-related indicators, that are readily available and inexpensive and can be considered as potential biomarkers for predicting PFS of MM underwent ASCT.

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Disclosure

The authors report no conflicts of interest in this work.

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