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Peripheral Absolute Lymphocyte Count: An Economical and Clinical Available Immune- Related Prognostic Marker for Newly Diagnosed Multiple Myeloma

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Background: To find economical and clinically available immune-related prognostic markers that could predict the overall survival (OS) of newly diagnosed multiple myeloma (NDMM) in the new drug era.

Material/Methods: Absolute lymphocyte count (ALC) and absolute monocyte count (AMC) were measured in routine blood samples from 102 patients with NDMM, and the lymphocyte-monocyte ratio (LMR) was derived. All the patients were receiving bortezomib-based chemotherapy as induction treatment. Log-rank testing was used for comparing the differences between groups. Univariate and multivariate tests were used to identify prognostic markers.

Results: The median ALC and LMR values at diagnosis were $1.43 \times 10^9/L$ and 3.7, respectively, and served as the cutoff point. As prognostic factors, ALC, LMR, and a new staging system combining ALC and the ISS staging system (L-ISS) were expected to have a significant impact on predicting OS. Furthermore, multivariate analysis showed that $ALC \geq 1.43 \times 10^9/L$ (hazard ratio [HR]: 0.223; 95% confidence interval [CI]: 0.071–0.705; $P=0.011$), $LMR \geq 3.7$ (HR: 0.363; 95% CI: 0.139–0.947; $P=0.038$), and L-ISS late stage (HR: 1.619; 95% CI: 1.065–2.743; $P=0.027$) were independent predictors for OS.

Conclusions: ALC and LMR can serve as surrogate markers for patients' antitumor immunity at the initial diagnosis of multiple myeloma. A new immune-related staging system, L-ISS, which combines ALC and the ISS staging system, can predict clinical outcomes in patients who are receiving bortezomib-based chemotherapy.

MeSH Keywords: **Lymphocyte Count • Multiple Myeloma • Prognosis**

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Background

Multiple myeloma (MM) is a common hematological malignant disease characterized by abnormal plasma cell proliferation and monoclonal immunoglobulin production. It is more common among the elderly, and it takes second place among hematological malignancies [1,2]. Early identification of high-risk groups and appropriate treatment regimens may increase the rate of remission and extend overall survival (OS) [3]. With the introduction of new drugs (protease inhibitor and immunomodulatory agents), disease prognosis has improved significantly in the last decade [4,5]. However, MM is still incurable, with a 52.2% 5-year OS rate based on data from the Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database 2009–2015. Currently, the international staging system (ISS) [6] and the Durie-Salmon (DS) staging system [7] are the main prognostic assessment systems for MM, but they do not account for host immunity or new drugs' effect. In recent years, antitumor immune status has been recognized as affecting patients' prognosis in many malignant diseases including hematological malignancy. During the same time period, it was found that absolute lymphocyte count (ALC) of peripheral blood could reflect host immune function and predict patients' prognosis in several diseases [8–11]. A reduced lymphocyte count is considered a poor prognostic factor in malignancy, suggesting an important role for immunosurveillance and clearance of lymphocytes [12]. The survival of MM cells depends on their interaction with the microenvironment [13]. A new prognostic evaluation system that incorporates immune-related biomarkers is urgently needed. Studies have shown that tumor-associated macrophages (TAMs) play a role in supporting MM cell growth, survival, and drug resistance in the pathogenesis of MM [14]. In several tumors, an elevation in the absolute monocyte count (AMC) of peripheral blood has been reported to be associated with a poor prognosis and could be considered a prognostic factor [15,16]. In addition, an elevation in the lymphocyte–monocyte ratio (LMR) is considered a good prognostic indicator for newly diagnosed MM (NDMM) patients [17]. Surui et al. [18] showed that the level of ALC had no significant effects on the outcome of MM patients treated with new drugs, although other research yielded the opposite conclusion. So, it is debatable whether ALC can be used as one of the criteria for evaluating the prognosis of patients taking new drugs. At present, there are few reports about the effect of ALC, AMC, and LMR on the treatment and prognosis of MM. In the current study, the effects of these 3 factors on OS in Chinese NDMM patients and the relationship between ALC and clinical parameters were analyzed retrospectively. We also explored whether ALC could function as an antitumor immune-related marker that has prognostic value for NDMM patients in the era of novel agents.

Material and Methods

General information

This study included 102 NDMM patients from January 1, 2014, to December 31, 2018, in Shengjing Hospital of China Medical University who were treated with bortezomib-based chemotherapy. The diagnosis was made according to the International Myeloma Working Group guidelines for symptomatic MM. All the patients were classified according to the staging criteria [6]. The patients had no immune deficiency disease and no history of transplantation, other malignant tumor, or prior immunosuppressive therapy. The following baseline data were collected: sex, age, body mass index (BMI), clinical stage, typing, hemoglobin (HGB) at first diagnosis, ALC, AMC, LMR, platelet count (PLT), lactate dehydrogenase (LDH), β 2-microglobulin (β 2-MG), serum albumin (ALB), serum calcium concentration, and immunoglobulin heavy chain (IgH) quantity. Univariate and multivariate analyses were done to find the clinical parameters that might affect OS.

Statistical analysis

OS was defined as the time from diagnosis to death (regardless of cause). Univariate analysis of survival was done by Kaplan-Meier curve, and multivariate Cox regression models were used to verify the association between multiple variables and prognosis. Log-rank test was used for making comparisons between groups. $P < 0.05$ was considered statistically significant. SPSS 26.0 software was used for data analysis.

Results

Patients' characteristics

Patients' baseline clinical and laboratory characteristics are listed in Table 1. There were 287 patients who received a diagnosis of MM during this period, and 102 patients were enrolled in the study. We excluded 185 patients as follows: 2 patients had a history of solid tumor, 13 patients received immunosuppressive therapy, 31 patients refused chemotherapy, and 139 patients received the traditional regimen without bortezomib. The median follow-up time was 427 (range: 5–1812) days. By the end of follow-up (February 10, 2019), 65 of the 102 enrolled patients (63.7%) were still alive.

The median peripheral blood ALC was 1.43 (range: 0.48 – 5.32) $\times 10^9/L$ at the time of initial diagnosis, which was considered as the cutoff point in our study. In order to determine whether ALC can enhance the prognostic effect of ISS, we divided 102 patients into 3 groups by combining ALC and ISS (L-ISS). The L-ISS staging system was defined as follows:

Table 1. The relationship between ALC and prognostic factors ($P<0.05$).

Characteristics	Low ALC group ALC $<1.43 \times 10^9/L$	High ALC group ALC $\geq 1.43 \times 10^9/L$	P-value
Sex			0.297
Male	36	31	
Female	15	20	
Age, y			0.003
<60	17	32	
≥ 60	34	19	
BMI, kg/m ²			0.992
<22.85	20	22	
≥ 22.85	21	23	
DS staging			0.13
Stage I	1	6	
Stage II	7	8	
Stage III	43	37	
Group A	31	43	0.008
Group B	20	8	
ISS staging			0.007
Stage I	1	4	
Stage II	12	24	
Stage III	38	23	
ISS dichotomy			0.002
Early stage	13	28	
Late stage	38	23	
L-ISS staging			<0.001
Stage I	0	5	
Stage II	12	44	
Stage III	39	2	
L-ISS dichotomy			<0.001
Early stage	12	49	
Late stage	39	2	
M-fraction type			0.644
IgG	24	25	
IgA	8	12	
Light chain	14	12	
Light chain type			0.231
κ	24	31	
λ	24	19	
HGB, g/L			<0.001
<100	44	27	
≥ 100	7	24	

Table 1 continued. The relationship between ALC and prognostic factors ($P<0.05$).

Characteristics	Low ALC group ALC $<1.43 \times 10^9/L$	High ALC group ALC $\geq 1.43 \times 10^9/L$	P-value
PLT			0.038
< $135 \times 10^9/L$	23	13	
$\geq 135 \times 10^9/L$	28	38	
LDH, U/L			0.971
<243	29	31	
≥ 243	20	22	
$\beta 2$ -MG, mg/L			0.004
<5.5	11	25	
≥ 5.5	37	24	
ALB, g/L			0.19
<35	35	29	
≥ 35	16	22	
Ca, mmol/L			0.065
<2.75	48	42	
≥ 2.75	3	9	
IgG dichotomy, g/L			0.26
<70	17	14	
≥ 70	6	10	
IgA dichotomy, g/L			0.848
<50	5	8	
≥ 50	3	4	

L-ISS stage I (good prognostic group): ALC $\geq 1.43 \times 10^9/L$ plus ISS stage I; L-ISS stage II (general prognostic group): neither I or III; and L-ISS stage III (poor prognostic group): ALC $<1.43 \times 10^9/L$ plus ISS stage III. In order to identify the effect of ALC among high-stage patients, we divided the patients into dichotomous groups. For both ISS and L-ISS, early stage included stage I and II and late stage was defined by stage III. Median values of AMC, LMR, and BMI were set as cutoff points as follows: AMC, $0.4 \times 10^9/L$; LMR, 3.7; and BMI, 22.85 kg/m².

The relationships between the prognostic factors and ALC are shown in Table 1. The low ALC group was significantly associated with older age, DS stage group B, stage III of ISS and L-ISS staging system, late ISS stage, late L-ISS stage, HGB <100 g/L, low PLT group, and high $\beta 2$ -MG group ($P<0.05$). No significant differences were found between the high and low ALC group with regard to sex, BMI, DS staging, M-fraction type, light chain type, LDH, ALB, serum calcium, and IgH quantity ($P>0.05$) (Table 1).

Analysis the effects of clinical parameters on OS by univariate analysis

The results showed that patients with low ALC (Figure 1A) and LMR (Figure 1B), L-ISS stage III (Figure 1C), and late stage of L-ISS (Figure 1D) and ISS (Figure 1E) had significantly shorter OS than others ($P<0.05$, Table 1). Meanwhile, patients with low IgG and ALB had longer OS than others ($P<0.05$, Table 2). There were no significant difference in OS between sex, age, BMI, DS staging, ISS staging, light chain type, AMC, HGB, PLT, LDH, $\beta 2$ -MG, calcium, and the quantity of immunoglobulin ($P>0.05$) (Table 2).

Relationship between OS and related factors in multivariate analysis

The results of the multivariate analysis of factors that might influence OS are shown in Table 3. The prognostic value of ALC, LMR, ALB, L-ISS dichotomy, and ISS dichotomy was assessed. The results showed that ALC $\geq 1.43 \times 10^9/L$ (HR: 0.223; 95% CI: 0.071–0.705; $P=0.011$), LMR ≥ 3.7 (HR: 0.363; 95% CI: 0.139–0.947; $P=0.038$), and L-ISS staging system (HR: 1.619;

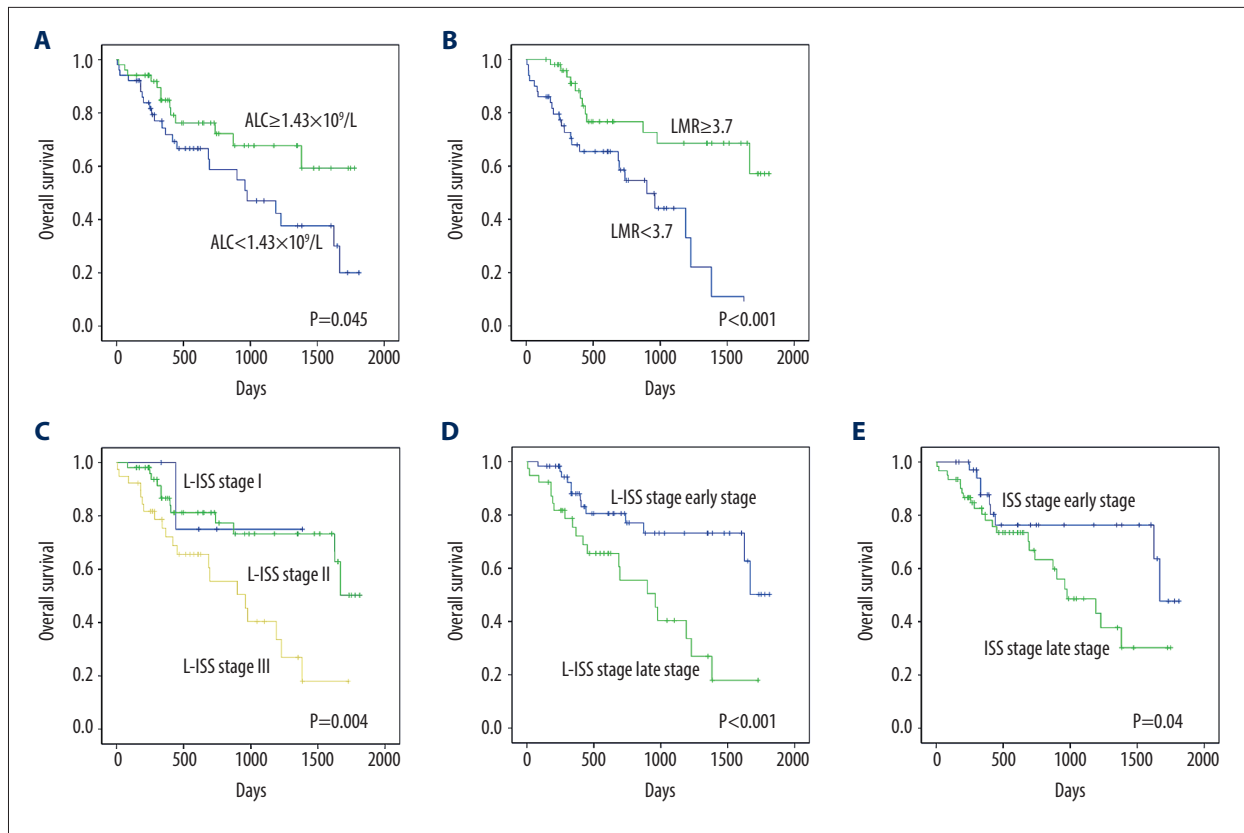


Figure 1. (A) $ALC < 1.43 \times 10^9/L$ predicted shorter OS. (B) $LMR < 3.7$ predicted shorter OS. (C) Patients in L-ISS stage III were predicted to have shorter OS. (D) Patients in late stage of L-ISS were predicted to have shorter OS. (E) Patients in late stage of ISS predicted to have shorter OS.

95% CI: 1.065–2.743; $P=0.027$) were still independent prognostic factors for predicting OS for the NDMM treated with a bortezomib-based regime (Table 3).

Discussion

Prediction of the prognosis in MM remains a challenge, despite commonly used prognostic tools such as the DS staging, ISS stage, and revised ISS (R-ISS) staging systems. These staging systems are based on tumor burden and tumor cytogenetics and thus neglect markers of immune dysfunction [19]. Under normal conditions, when tumor cells are present in the body, the immune system recognizes them due to their heterogeneity and produces an immune response [20]. Individual differences in immune condition could affect patients' prognosis. Currently, immune function tests are costly and cannot be performed in some hospitals. A cost-effective and widely available clinical test that can predict progression is needed.

Lymphocytes represent an important cellular component of the body's immune response, and they include several subgroups, each of which plays a different role; consequently,

the antitumor immune response associated with lymphocytes is very complex [21,22]. Changes in immunologic and inflammatory biomarkers, such as the ratio of peripheral blood neutrophils to lymphocytes, have been shown to affect clinical outcomes [23–25]. Although ALC does not represent the whole picture of the immunologic anti-tumor mechanism and the function and quantity of subsets, it can be used as an important index of immune function [26]. Monocytes can reduce the antitumor ability of the host and promote the survival and proliferation of tumor cells, which is regarded as an indicator of poor prognosis. The underlying mechanism is still being investigated, but one of the observations is that tumor-derived chemotactic factors recruit circulating monocytes to the tumor site. These monocytes are identified as TAMs [27], and they have been shown to play an important role in tumor cell growth, angiogenesis, and metastasis [28]. Previous research found that the peripheral blood AMC can serve as a surrogate marker for TAMs [29,30]. ALC is also an important marker of immune remodeling after autologous stem cell transplant, and the level of ALC recovery after transplant is an independent prognostic factor [8]. *In vitro* studies showed that B and T lymphocytes were inhibited by MM cells, indicating that ALC is associated with disease severity. In our study,

Table 2. Univariate analysis of the influence of clinical parameters on OS in MM patients ($P < 0.05$).

Characteristics	n	OS, %	P-value	
Sex	Male	67	62.7	0.805
	Female	35	65.7	
Age, y	<60	49	71.4	0.083
	≥60	53	56.6	
BMI, kg/m ²	<22.85	42	66.7	0.335
	≥22.85	44	75.0	
DS staging	Stage I	7	85.7	0.138
	Stage II	15	66.7	
	Stage III	80	61.3	
	Group A	74	67.6	
	Group B	28	53.6	
ISS staging	Stage I	5	100	0.088
	Stage II	36	71.9	
	Stage III	61	60.7	
ISS dichotomy	Early stage	41	75.7	0.04
	Late stage	61	60.7	
L-ISS staging	Stage I	5	80	0.004
	Stage II	56	75	
	Stage III	41	46.3	
L-ISS dichotomy	Early stage	61	78	<0.001
	Late stage	41	48.7	
M-fraction type	IgG	49	75.5	0.004
	IgA	20	65	
	Light chain	26	46.2	
Light chain type	κ	55	60	0.519
	λ	43	72.1	
ALC	<1.43×10 ⁹ /L	51	52.9	0.045
	≥1.43×10 ⁹ /L	51	74.5	
AMC	<0.4×10 ⁹ /L	52	67.3	0.284
	≥0.4×10 ⁹ /L	50	60.0	
LMR	<3.7	50	50.0	<0.001
	≥3.7	52	76.9	
HGB, g/L	<100	71	60.6	0.142
	≥100	31	71.0	
PLT	<135×10 ⁹ /L	36	61.1	0.381
	≥135×10 ⁹ /L	66	65.2	
LDH, U/L	<243	60	58.3	0.914
	≥243	42	60.0	

Table 2 continued. Univariate analysis of the influence of clinical parameters on OS in MM patients ($P < 0.05$).

Characteristics	n	OS, %	P-value
β2-MG dichotomy, mg/L	<5.5	36	77.8
	≥5.5	61	60.7
ALB, g/L	<35	64	69.8
	≥35	38	55.3
Ca, mmol/L	<2.75	90	64.4
	≥2.75	12	58.3
IgG dichotomy, g/L	<70	31	80.6
	≥70	16	68.8
IgA dichotomy, g/L	<50	13	76.9
	≥50	7	42.9

Table 3. Relationship between OS and related factors in the multivariate analysis ($P < 0.05$).

	P-value	HR (95% CI)
ALC $\geq 1.43 \times 10^9/L$	0.011	0.223 (0.071–0.705)
LMR ≥ 3.7	0.038	0.363 (0.139–0.947)
ALB ≥ 35 g/L	0.311	0.564 (0.186–1.709)
L-ISS late stage	0.027	1.619 (1.065–2.743)
ISS late stage	0.624	0.699 (0.167–2.928)

patients with a low ALC were elderly, had advanced stage disease, and had severe anemia, which aligned with the previous study. Ege et al. [31] analyzed 537 MM patients retrospectively and found a significantly longer OS for MM patients with ALC $\geq 1.4 \times 10^9/L$ compared with those with ALC $< 1.4 \times 10^9/L$ (65 vs. 26 months, $P < 0.0001$), which indicated that ALC was an important prognostic factor in NDMM at initial diagnosis. Other studies indicated that low ALC ($< 1.6 \times 10^9/L$) at initial diagnosis of MM patients predicted shorter OS and LMR > 4 predicted better survival tendency [18].

Taken together, the levels of ALC, AMC, and LMR might be considered as being representative of the host immune system. Therefore, our study was performed to identify whether peripheral blood ALC, which represents the patient's immunity, and AMC, which represents the tumor microenvironment, combined with LMR had prognostic significance for MM.

The prognostic impact of ALC, AMC, and LMR in NDMM patients treated with bortezomib-based chemotherapy was retrospectively evaluated in the present study. The results showed that both ALC $\geq 1.43 \times 10^9/L$ and LMR ≥ 3.7 were associated with longer OS and were also independent predictors for OS in a

multivariate analysis. The state of the immune system should therefore be carefully monitored as a potential variable influencing outcome in MM patients. AMC was not significantly associated with OS, suggesting that AMC alone does not represent a prognostic factor for MM patients. Overall, ALC and LMR were independent predictors, whereas AMC was not, indicating ALC could predict prognosis for MM patients. In addition, ALC is a surrogate marker of host immune function. So, we explored whether a new staging system incorporating patients' initial immune function could identify high-risk MM patients. We combined the level of ALC and the ISS staging system into the L-ISS staging system, and we found that it further defined MM patients' prognosis. The L-ISS staging system potentially improved the predictive value for NDMM patients being treated with bortezomib-based chemotherapy, which verified that the initial immune function was important.

However, some limitations were present in our study. Our results were based on a single-center analysis in China and the number of enrolled patients was not large. Moreover, these patients did not have test results for the lymphocyte subsets, including levels of CD8⁺ and CD4⁺ T cells and NK cells, to clearly define their immune status. In future studies, lymphocyte subsets should be quantified to clarify details about immune function (e.g., T cells, B cells, or NK cells) and their relationship with prognosis of MM patients.

Although these weaknesses existed, our study demonstrated that the ALC and LMR at diagnosis could be reveal the MM patients' initial immune status and be related with prognosis. A multicenter study is still required to verify if this finding applies to more patients.

Conclusions

The treatment of MM has gone through the traditional treatment era and the new drugs era, and it is currently in the era of immunotherapy. Focusing on MM patients' host immune function is quite important. ALC at initial diagnosis, an economical and clinically available index reflecting host systemic immunity, could predict NDMM patients' prognosis in

the bortezomib era. Owing to the significant prognostic value of ALC in NDMM, further studies on ALC, LMR, and even lymphocyte subsets could be conducted to better understand the immune-related role in individuals with MM.

Conflict of interest

None.

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