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Can the prognosis of mantle cell lymphoma be predicted by simple CBC counts?

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Abstract

Mantle cell lymphoma (MCL) exhibits a heterogenous clinical course. The MCL International Prognostic Index (MIPI) is the most commonly used risk classification system in MCL. However, it does not contain a parameter associated with the tumor microenvironment. The aim of this study was to develop a more powerful prognostic index by evaluating the absolute monocyte count (AMC), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) at diagnosis in conjunction with the clinical and laboratory parameters.

The data of 96 MCL patients with newly diagnosed from January 2014 to December 2018 were retrospectively evaluated in this study. The AMC, NLR, and PLR cut-off values were determined using the receiver operating characteristic (ROC) analysis.

The clinical behavior and results of the disease exhibited significant variation in high and low value groups at the time of diagnosis. In univariate analysis, the AMC ≥ 580, NLR ≥ 2.43, and PLR ≥ 120.85 were determined as negative prognostic factors for 5-year progression free survival (PFS) (AMC: PFS, $P < .001$; NLR: PFS, $P < .001$; PLR: PFS, $P < .001$) and for 5-year overall survival (OS) ($P < .001$, $P < .001$, $P < .001$, respectively). Beta-2 microglobulin (B2-MG), and MIPI for PFS, and for OS were found to be independent risk factors in the multivariate analysis (for PFS: $P = .006$, $P = .002$, respectively; and for OS: $P = .007$, $P = .001$, respectively). The 5-year OS was 20% in the group with B2-MG ≥ 3.5. The patients in high-risk MIPI group had poorer 5-year OS (median OS: 40 months, $P < .001$).

The results stated that the use of B2-MG in conjunction with MIPI was a more sensitive method in determining the prognosis in MCL (median OS: 12 months in high-risk MIPI group with a B2-MG ≥3.5, $P < .001$). Additionally, it was found that parameters reflecting the tumor microenvironment such as AMC, NLR, and PLR increased the risk of progression in MCL. In view of these findings, in addition B2-MG to the MIPI to create a more sensitive prognostic scoring system may provide an insight into personalization of treatment with early recognition of patients with poor prognosis.

Abbreviations: AMC = absolute monocyte count, B2-MG = beta-2 microglobulin, CR = complete response, CRP = C-reactive protein, DLBCL = diffuse large B-cell lymphoma, ECOG-PS = Eastern Cooperative Oncology Group performance score, EDTA = ethylene diamine tetra acetic acid, ESR = erythrocyte sedimentation rate, FCM = flow cytometry, FL = follicular lymphoma, IGHV = immunoglobulin heavy chain, LDH = lactate dehydrogenase, MCL = mantle cell lymphoma, MIPI = mantle cell lymphoma international prognostic index, NHL = non-Hodgkin lymphomas, NLR = neutrophil/lymphocyte ratio, NR = no response, OS = overall survival, PD = progressive disease, PFS = progression free survival, PLR = platelet/lymphocyte ratio, PR = partial response, ROC = receiver operating characteristic, SD = stable disease, TAM = tumor-associated macrophages, TGF-β = transforming growth factor-β.

Keywords: AMC, B2-microglobulin, mantle cell lymphoma, MIPI, NLR, PLR, prognosis

1. Introduction

Mantle cell lymphoma (MCL) is a different sub-type of B-cell non-Hodgkin Lymphomas (NHL), and accounts for 5% to 10% of all malignant lymphomas.[1] The clinical course and treatment responses exhibit heterogeneity in MCL. Although the disease responds well to the first-line treatment, MCL has shorter survival rate compared to other lymphomas due to the high frequency of relapse.[2] Although most patients have a poor prognosis, some cases have an indolent clinical course and it does not require treatment for a long time after the diagnosis.[3] Due to the variations in the clinical course of this disease, several prognostic parameters that constitute predictive value in the diagnosis as well as the treatment decision and selection of the treatment have been defined. The Ki-67 index,[4] that is indicative of the cell proliferation rate and SOX11 expression[5] have been described as pathologic prognostic markers; whereas TP-53 expression,[6] MYC overexpression[7] and the mutational status of immunoglobulin heavy chain (IGHV)[8] have been described

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as genetic prognostic markers. However, these parameters are subject to interobserver variations due to the lack of a standardized approach between different laboratories, which limits their predictive value. Moreover, they are expensive and impractical to use. Therefore, the MCL International prognostic index (MIPI) has been developed in order to define the disease risk groups. MIPI is the first defined clinical risk classification system and has demonstrated prognostic significance in MCL.[9] However, there are also contradictory results about the predictive value of MIPI in the previous studies.[10,11] MIPI is particularly insufficient in identifying the patients with a poor prognosis and studies to enhance the capacity of MIPI are still ongoing. The prognostic significance of parameters such as beta-2 microglobulin level (B2-MG),[12] albumin level and bone marrow infiltration [13] and Ki-67 index[3] in MCL has been demonstrated in some studies and it was suggested to make a revision by including these parameters in the current MIPI. However, a standardized revised MIPI description still does not exist.

The interaction between neoplastic tumor cells and their microenvironment have been studied in recent years and it was shown that not only genetic abnormalities, but also various components in the tumor microenvironment had an effect on the development and progression of lymphoma. Lymphocytes that infiltrate the tumor play a role in the immune response to cancer and tumor- associated macrophages (TAM) play a role in angiogenesis. Neutrophils suppress the cytolytic activity of lymphocytes, whereas platelets suppress the number of lymphocytes by secreting anti-inflammatory cytokines such as the transforming growth factor-β (TGF-β) and create an immunosuppressive effect.[14,15] In other words, peripheral blood cells such as lymphocytes, neutrophils, platelets, and monocytes reflect the systemic inflammatory response and the host immune response to the tumor. It is thought that they can contribute to the risk assessment in lymphomas.

Therefore, the relationship of the isolated/combined use of these parameters with disease progression and survival has been studied in several lymphoma sub-groups. It has been demonstrated that lymphocyte/monocyte ratio (LMR) and neutrophil/lymphocye ratio (NLR) have prognostic significance in Follicular Lymphoma (FL).[16] The prognostic value of LMR and platelet/lymphocyte ratio (PLR) has been investigated in 173 patients who were diagnosed with Primary Gastrointestinal Diffuse Large B-cell lymphoma (DLBCL), wherein NLR was described as an independent prognostic factor for survival; however, a relationship between PLR and the course of the disease was not observed.[17] On the other hand, absolute monocyte count (AMC) was demonstrated to be a reliable prognostic marker in DLBCL[18] and FL.[19] Von Hohenstaufen et al were the first to report that AMC could be used as an independent prognostic factor in MCL.[20] The prognostic significance of AMC in MCL was then demonstrated in a limited number of studies.[21,22] However, there was no association between AMC and survival in some studies.[23] The prognostic significance of NLR and PLR in MCL is yet to be investigated. This study is the first research that investigates prognostic significance of NLR and PLR, which indicates systemic inflammatory response, in addition to AMC in MCL patients and aims to evaluate AMC, NLR, and PLR in conjunction with the clinical and laboratory parameters in order to assess their effect on progression- free survival (PFS) and overall survival (OS) to improve risk classifications.

2. Materials and methods

2.1. Patient selection

Niety-six MCL patients with newly diagnosed and followed up from January 2014 to December 2018, and received at least two cycles of first-line treatment regimen were included in the study. Patients' clinical parameters (age, gender, Eastern Cooperative Oncology Group performance score (ECOG- PS), bone marrow infiltration, stage, extranodal disease, laboratory parameters (serum lactate dehydrogenase (LDH), beta-2 microglobulin (B2-MG), C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), response to treatment and risk classification (MIPI) were carefully recorded at the time of diagnosis from the patient files. The AMCs were determined from routine complete blood count with three-part differential counts (lymphocytes, neutrophils, thyrombocytes) obtained at the time of diagnosis of MCL using Sysmex automated hematology analyzers (Sysmex XN 9000). Measurement was repeated by flow cytometry (FCM) analysis to verify AMCs. Then, peripheral blood samples were collected from ethylene diamine tetra acetic acid (EDTA) containing tubes, and the samples were incubated with antibodies against CD14, and CD45 (Beckman Coulter, Marseille, France). Appropriate isotype-matched negative controls were used in the monoclonal antibody panel to assess background fluorescence intensity. A 100 μL blood samples was incubated with the monoclonal antibodies at room temperature for 15 min and 1 mL VersaLyse (Beckman Coulter) was added for 10 min. Finally, 10.000 cells were acquired from the tubes on the FCM device (Navios 2L6C; Beckman Coulter) and analysed using Navios software (Kaluza 1.5a). After acquiring the cells, the CD45/side scatter (SS) log scale was selected to eliminate debris and analyse the cells. Total leukocytes were gated as CD45 positive cells. Monocytes were selected by using CD14/SSC graphic. Thus, localization of monocytes was determined by back-gating in CD45/SSC. Six patients who were diagnosed with the blastoid variant and had an active infection at the time of diagnosis were excluded from the study. During the first-line treatment, 70 patients received Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP), 8 patients received Rituximab-Bendamustine (R-B), and 18 patients received Rituximab, Cyclophosphamide, Vincristine, Adriamycin, Dexamethasone, Methotrexate (R-HyperCVAD A+B) protocol. Sixteen patients underwent high dose chemotherapy followed by Autologous Bone Marrow Transplantation as primary therapy. Two patients underwent Allogeneic Bone Marrow transplantation due to relapse/refractory disease. Patients' data was presented retrospectively. This study was conducted after obtaining an approval from Gaziantep University Medical Faculty Medical Ethics Committee, and informed consent was obtained from the patients.

2.2. Follow-up

Regular radiographic and laboratory examinations were performed after treatment, and disease status was determined and recorded. The primary endpoint of the study was OS and PFS. OS was accepted as the time from diagnosis to death/last visit, and PFS was accepted as the time from diagnosis to the first progression/death from any cause/last visit. Response to first-line treatment was grouped as complete response (CR) and other responses (partial response [PR], stable disease [SD], no response [NR] and progressive disease [PD]).

2.3. Statistical analysis

In this study, three logistic models were planned in order to assess the importance of NLR, PLR, and AMC in predicting mortality. NLR, PLR, and AMC were described as continuous independent variables and the end point was described as cancer-related death. The cut-off values for NLR, PLR, and AMC were obtained using the receiver operating characteristic (ROC) analysis method, and cut-off values of laboratory parameters were based on the upper/lower limit of the local laboratory. A chi-square test was used in comparing the characteristics of the patients in high and low NLR, PLR, and AMC groups. The Kaplan-Meier method was used for PFS and OS analysis, and the Log-rank test was used to compare the lifespans in PFS and OS according to NLR, PLR, and AMC. Cox regression analysis was used in the univariate and multivariate analyses. $P < .05$ is considered statistically significant. Count, percentage, mean, median, and standard deviation values of the data were calculated. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) software was used in the analysis of all study data.

3. Results

3.1. Patients' clinical characteristics

A total of 96 patients, i.e. 20 females and 76 males, were included in the study. Six patients with blastoid variant and had an active infection at the time of diagnosis were excluded from the study. The median age of the patients was 63.5 years (range 29–83 years), and the median duration of follow-up was 31 months (range 3–170 months). During follow-up, 53 patients (55.2%) died due to relapsed/refractory lymphoma. The 5-year median OS was 40 months in the patients included in this study (95% CI: 33.18–46.82 months). 56 (58.3%) patients had progression after first-line treatment and the median time until progression was 21 months (range 2–170 months). The 5-year median PFS was 30 months (95% CI: 23.45–36.55 months). The 5-year OS rate and 5-year PFS rate were 40.3% and 33.5%, respectively.

3.2. Comparison of patient grouping by using the cut-off values of AMC, NLR, and PLR

The cut-off value of AMC, NLR, and PLR were selected using the ROC analysis, and the following values were found: AMC optimal cut-off value 580 ($P < .001$; AUC = 0.666; sensitivity = 62.26% (95% confidence interval [CI]: 47.9–75.2); specificity = 69.77% [95% CI 53.9–82.8]), NLR optimal cut-off value 2.43 ($P < .001$; AUC = 0.725; sensitivity = 67.92% [95% CI: 53.7–80.1]; Specificity = 72.09% [95% CI 56.3–84.7]), PLR optimal cut-off value 120.85 ($P < .001$; AUC = 0.713; sensitivity = 75.47% [95% CI: 61.7–86.2], specificity = 69.77% [95% CI 53.9–82.8]). The patients were categorized into two groups based on NLR, PLR, and AMC variables, i.e. high NLR (≥2.43) and low NLR (<2.43), high AMC (≥580) and low AMC (<580), high PLR (≥120.85) and low PLR (<120.85).

Characteristics of the patients in high and low value groups are summarized in Table 1. Clinical and laboratory parameters were compared between the groups. There were 49 (51.0%) and 47 (49.0%) patients in high and low NLR groups, respectively. There were significant differences between the high and low NLR groups in terms of patient characteristics. High NLR group was associated with advanced age (≥60 years; 28.5% vs 55.4%, $P = .008$), elevated LDH (61.2% vs 27.2%, $P = .002$), high CRP (CRP > 5; 71.5% vs 48.9%, $P = .02$), high risk MIPI (38.8% vs 31.9%, $P = .003$), and poor treatment response (non-CR; 53.1% vs 29.7%, $P = .02$). There were 46 (47.9%) and 50 (52.1%) patients in the high and low AMC groups, respectively. A comparison of the AMC (≥580) and AMC (<580) groups revealed that high AMC was associated with male gender (91.3% vs 68%, $P = .005$), worse ECOG-PS (ECOG-PS 2-3; 50% vs 24%, $P = .008$), elevated LDH (LDH; 60.9% vs 32%, $P = .005$), elevated CRP (CRP > 5; 80.4% vs 42%, $P < .001$), high B2-MG (B2-MG ≥ 3.5; 71.7% vs 50%, $P = .03$) and high index of risk classification (high-MIPI; 37% vs 34%, $P = .01$). Based on the PLR variable, there were 43 (44.8%) and 53 (55.2%) patients in low and high PLR groups, respectively. A comparison of the group with PLR (<120.85) and the group with PLR (≥120.85) showed that high PLR was associated with advanced age (≥60 years; 69.8% vs 44.1%, $P = .01$), advanced Ann Arbor stage (stage ≥ 2; 83% vs 65.1%, $P = .04$), elevated LDH (56.6% vs 32.5%, $P = .01$), high risk MIPI (41.5% vs 27.9%, $P = .003$) and poor treatment response (non-CR; 52.9% vs 28%, $P = .01$, Table 1).

3.3. Survival

The group with AMC ≥ 580×10^9/L was compared with AMC < 580×10^9/L group. In the group with high AMC, the 5-year PFS and 5-year OS were 13.1% and 19.1% respectively, whereas in the group with low AMC values, the 5-year PFS and 5-year OS were 49.5% and 50%, respectively. Pretreatment high AMC was found to be associated with poorer 5-year PFS (mean PFS for AMC ≥ 580: 19.0 ± 4.57, 95% CI = 10.03–27.96, $P < .001$; Fig. 1a) and poorer 5-year OS (median OS for AMC ≥ 580: 31.0 ±2.56, 95% CI = 25.98–36.02, $P < .001$; Fig. 1b).

The group with a NLR ≥ 2.43 had poorer 5-year PFS (median PFS for NLR ≥ 2.43: 21.0±3.81, 95% CI = 13.53–28.47, $P < .001$; Fig. 2a) and a clearly poorer 5-year OS (median OS for NLR ≥ 2.43: 31.0±1.54, 95% CI = 27.96–34.03, $P < .001$; Fig. 2b). In the group with NLR ≥ 2.43, the 5-year PFS and 5-year OS were 11.9% and 12.3% respectively, whereas in the group with low NLR, the 5-year PFS and 5-year OS were 54.8% and 67.4%, respectively.

PLR is another index that shows peripheral blood cell circulation. PLR ≥ 120.85 indicates a poor prognosis (5-year PFS, 10.1% vs 57.6%, 5-year OS 12.3% vs 67.4%; both $P < .001$; Fig. 3a and b, respectively).

The clinical and laboratory parameters that affect OS and PFS were evaluated using univariate and multivariate analysis. Elevated CRP ($P = .004$), high Ki-67 ($P < .001$), AMC ≥ 580 ($P = .001$), NLR ≥ 2.43 ($P = .001$) and PLR ≥ 120.85 ($P = .003$) were found to be associated with poorer PFS; whereas elevated ESR (>40), B2-MG (≥3.5) and high risk MIPI status were determined to be independent risk factors for PFS (HR = 2.09; 95% CI: 1.11–3.92, $P = .02$; HR = 2.66; 95% CI: 1.32–5.36, $P = .006$; HR = 3.99; 95% CI: 1.69–9.42, $P = .002$, respectively). A comparison of the high and low-risk MIPI risk status at the time of diagnosis revealed that a high risk status was associated with 8.18 fold increased risk of progression, wherein AMC ≥ 580, NLR ≥ 2.43 and PLR ≥ 120.85 were associated with a 2.84, 2.77, and 2.41 fold increased risk of progression. It was found that the patients with AMC ≥ 580 were more predisposed to poorer PFS, compared to the patients with AMC < 580; however, statistical significance was not reached in

Table 1

Patients' characteristics and treatment response.

		NLR			AMC			PLR		
		<2.43	≥2.43		<580	≥580		<120.85	≥120.85	
	n = 96 n (%)	n = 47 (49.0)	n = 49 (51.0)	*P*	n = 50 (52.1)	n = 46 (47.9)	*P*	n = 43 (44.8)	n = 53 (55.2)	*P*
Age										
≤60	40 (41.7)	26 (55.4)	14 (28.5)	.008	24 (48.0)	16 (34.8)	.18	24 (55.9)	16 (30.2)	.01
>60	56 (58.3)	21 (44.6)	35 (71.5)		26 (52.0)	30 (65.2)		19 (44.1)	37 (69.8)	
Gender										
Male	76 (79.2)	39 (83.0)	37 (75.5)	.36	34 (68.0)	42 (91.3)	.005	37 (86.0)	39 (73.5)	.13
Female	20 (20.8)	8 (17.0)	12 (24.5)		16 (32.0)	4 (8.7)		6 (14.0)	14 (26.5)	
ECOG-PS										
0-1	61 (63.5)	34 (72.4)	27 (55.1)	.07	38 (76.0)	23 (50.0)	.008	31 (72.0)	30 (56.6)	.11
≥2	35 (36.5)	13 (27.6)	22 (44.9)		12 (24.0)	23 (50.0)		12 (28.0)	23 (43.4)	
Bone marrow infiltration										
No	56 (58.3)	28 (59.6)	28 (57.1)	.80	28 (56.0)	28 (60.9)	.62	29 (67.5)	27 (50.9)	.10
Yes	40 (41.7)	19 (40.4)	21 (42.9)		22 (44.0)	18 (39.1)		14 (32.5)	26 (49.1)	
Ann Arbor stage										
I–II	24 (25.0)	14 (29.8)	10 (20.4)	.28	15 (30.0)	9 (19.6)	.23	15 (34.9)	9 (17.0)	.04
III–IV	72 (75.0)	33 (70.2)	39 (79.6)		35 (70.0)	37 (80.4)		28 (65.1)	44 (83.0)	
Ekstranodal involvement										
No	58 (60.4)	31 (66.0)	27 (55.1)	.27	30 (60.0)	28 (60.9)	.93	29 (67.4)	29 (54.7)	.20
Yes	38 (39.6)	16 (34.0)	22 (44.9)		20 (40.0)	18 (39.1)		14 (32.6)	24 (45.3)	
LDH										
Normal	52 (54.2)	33 (70.3)	19 (38.8)	.002	34 (68.0)	18 (39.1)	.005	29 (67.5)	23 (43.4)	.01
Elevated	44 (45.8)	14 (29.7)	30 (61.2)		16 (32.0)	28 (60.9)		14 (32.5)	30 (56.6)	
Treatment response										
CR	56 (58.3)	33 (70.3)	23 (46.9)	.02	33 (66.0)	23 (50.0)	.11	31 (72.0)	25 (47.1)	.01
Other	40 (41.7)	14 (29.7)	26 (53.1)		17 (34.0)	23 (50.0)		12 (28.0)	28 (52.9)	
MIPI										
Low	34 (35.4)	24 (51.1)	10 (20.4)	.003	24 (48.0)	10 (21.8)	.01	23 (53.5)	11 (20.7)	.003
Intermediate	34 (35.4)	15 (31.9)	19 (38.8)		17 (34.0)	17 (37.0)		12 (27.9)	22 (41.5)	
High	28 (29.2)	8 (17.0)	20 (40.8)		9 (18.0)	19 (41.2)		8 (18.6)	20 (37.8)	
CRP										
0–5	38 (39.6)	24 (51.1)	14 (28.5)	.02	29 (58.0)	9 (19.6)	<.001	21 (48.8)	17 (32.0)	.09
>5	58 (60.4)	23 (48.9)	35 (71.5)		21 (42.0)	37 (80.4)		22 (51.2)	36 (68.0)	
ESR										
0–40	60 (62.5)	31 (66.0)	29 (59.1)	.49	29 (58.0)	31 (67.4)	.34	28 (65.1)	32 (60.4)	.63
>40	36 (37.5)	16 (34.1)	20 (40.9)		21 (42.0)	15 (32.6)		15 (34.9)	21 (39.6)	
B2-MG										
<3.5	38 (39.6)	23 (48.9)	15 (30.6)	.06	25 (50.0)	33 (71.7)	.03	19 (44.1)	19 (35.8)	.40
≥3.5	58 (60.4)	24 (51.1)	34 (69.4)		25 (50.0)	33 (71.7)		24 (55.9)	34 (64.2)	

B2-MG = beta-2 microglobulin, CR = complete remission, CRP = C-reactive protein, ECOG-PS = Eastern Cooperative Oncology Group performance score, ESR = erythrocyte sedimentation rate, LDH = lactate dehydrogenase, MIPI = Mantle Cell Lymphoma International Prognostic index.

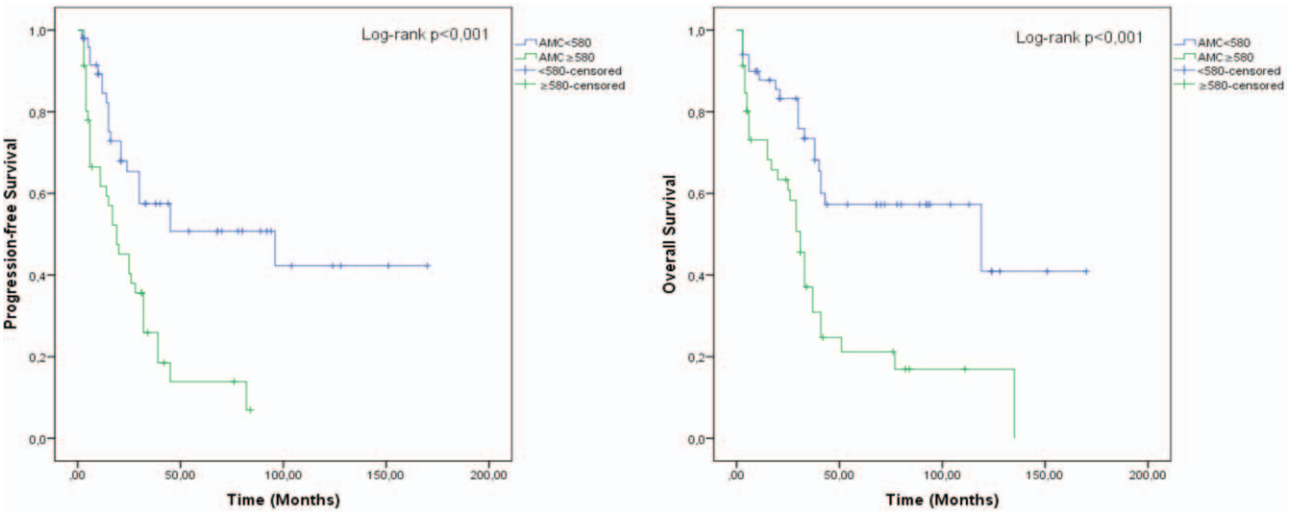

Figure 1. Survival. (A) PFS and (B) OS according to AMC. AMC = absolute monocyte count, PFS = progression free survival, OS = overall survival.

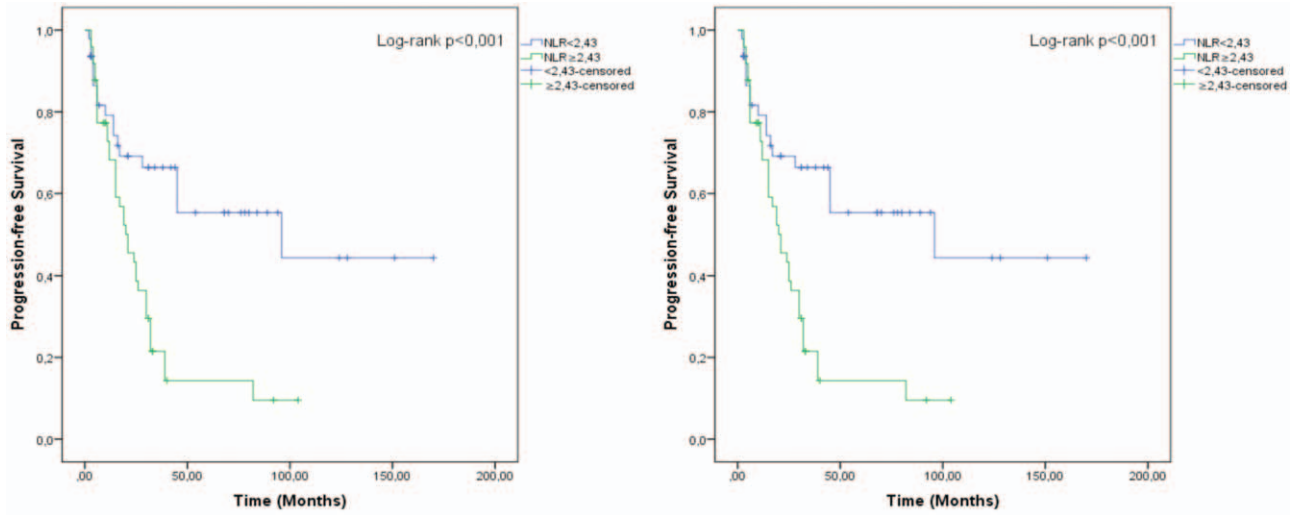

Figure 2. Survival. (A) PFS and (B) OS according to NLR. NLR = neutrophil/lymphocyte ratio, PFS = progression free survival, OS = overall survival.

the multivariate analysis (HR = 1.99; 95% CI: 0.94–3.89, Table 2).

An elevated CRP ($P = .004$), Ki-67 ($P < .001$), AMC ≥ 580 ($P = .001$) NLR ≥ 2.43 ($P < .001$) and PLR ≥ 120.85 ($P < .001$) were associated with poorer OS, whereas an elevated B2-MG (≥3.5) at the time of diagnosis and high-risk MIPI were determined to be independent risk factors for OS (HR = 2.73; 95% CI: 1.31–5.69, $P = .007$; HR = 6.65; 95% CI: 2.14–20.68, $P = .001$, respectively, Table 3).

There was a significant correlation between the MIPI score of the patients at the time of diagnosis and OS. Patients in the high-risk MIPI group had poorer 5-year OS (median OS for high risk MIPI: 40 months (95% CI: 33.18–46.81), $P < .001$, Fig. 4a) and poorer 5-year PFS (median PFS for high risk MIPI: 30 months (95% CI: 23.45–36.54, $P < .001$, Fig. 4b) in comparison to those in the intermediate or low risk group.

A high B2-MG ≥ 3.5 level at the time of diagnosis was associated with poorer 5-year OS and poorer 5-year PFS (5-year OS, 20% vs 69.7%; $P < .001$; 5-year PFS, 12.6% vs 59.8%; $P < .001$, Fig. 5a and b, respectively).

In the following section of the study, it was investigated whether the combined use of MIPI and B2-MG, which were determined to be independent prognostic factors for both PFS and OS, provided additional prognostic benefits for risk classification. The patients were assigned to two groups, i.e. low or intermediate risk and high-risk patients, in order to evaluate the predictive value of MIPI. Patients in the MIPI low/intermediate risk group with B2-MG ≥ 3.5 had poorer OS (the median OS for MIPI low/intermediate risk group with B2-MG ≥ 3.5 was 41 months [95% CI: 39.81–42.18]; $P < .001$, Fig. 6a) as compared to the patients in the MIPI low/intermediate risk group with B2-MG < 3.5. Patients in the MIPI high risk group with B2-MG ≥ 3.5 had significantly poorer OS as compared to the patients in the MIPI high risk group with B2-MG < 3.5 (median OS for MIPI high risk group with B2-MG ≥ 3.5 was 12 months (95% CI: 6.42–18.77); $P < .001$, Fig. 6b) (data not shown).

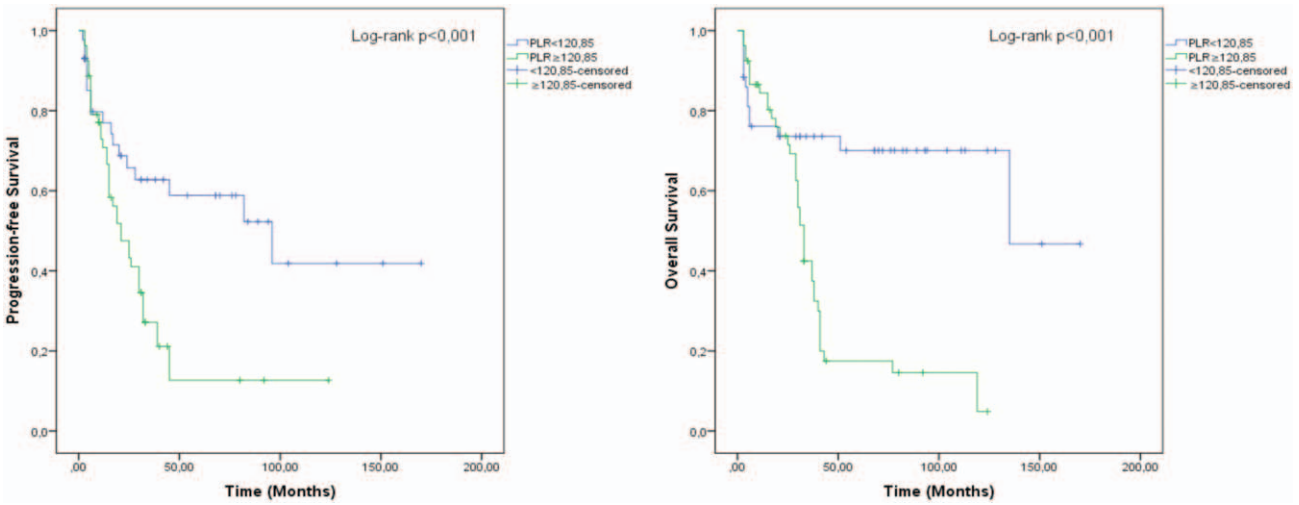

Figure 3. Survival. (A) PFS and (B) OS according to PLR. PLR = platelet/lymphocyte ratio, PFS = progression free survival, OS = overall survival.

Table 2

Cox regression univariate and multivariate analysis for progression free survival.

	Univariate analysis		Multivariate analysis	
	P	HR (95.0% CI)	*P*	HR (95.0% CI)
ESR	.005	2.16 (1.26–3.69)	.02	2.09 (1.11–3.92)
CRP	.004	2.61 (1.36–5.02)	.14	1.87 (0.81–4.31)
B2-MG	<.001	4.18 (2.16–8.11)	.006	2.66 (1.32–5.36)
Ki-67	<.001	3.82 (2.17–6.73)	.89	0.95 (0.49–1.85)
MIPI	.001	8.18 (3.76–17.80)	.002	3.99 (1.69–9.42)
AMC	.001	2.84 (1.61–5.02)	.05	1.91 (0.94–3.89)
NLR	.001	2.77 (1.55–4.95)	.55	1.25 (0.59–2.62)
PLR	.003	2.41 (1.34–4.33)	.57	1.30 (0.51–3.31)

AMC = absolute monocyte count, B2-MG = beta-2 microglobulin, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, MIPI = Mantle cell lymphoma International prognostic index, NLR = netrophil/lymphocyte ratio, PLR = platelet/lympocyte ratio.

Table 3

Cox regression univariate and multivariate analysis for overall survival.

	Univariate analysis		Multivariate analysis	
	P	HR (95.0% CI)	*P*	HR (95.0% CI)
ESR	.12	1.54 (0.89–2.66)	.63	0.86 (0.47–1.56)
CRP	.004	2.61 (1.36–5.02)	.05	2.25 (0.97–5.23)
B2-MG	<.001	4.18 (2.16–8.11)	.007	2.73 (1.31–5.69)
Ki-67	<.001	3.82 (2.17–6.73)	.85	1.06 (0.52–2.17)
MIPI	<.001	7.03 (2.75–17.93)	.001	6.65 (2.14–20.68)
AMC	.001	2.84 (1.61–5.02)	.56	1.20 (0.63–2.31)
NLR	<.001	3.30 (1.75–6.20)	.10	0.40 (0.13–1.19)
PLR	<.001	3.54 (1.84–6.83)	.41	1.37 (0.64–2.95)

AMC = absolute monocyte count, B2-MG = beta-2 microglobulin, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, MIPI = Mantle cell lymphoma International prognostic index, NLR = netrophil/lymphocyte ratio, PLR = platelet/lympocyte ratio.

4. Discussion

This study is the first and only comprehensive study that evaluates prognostic significance of the immunological markers which show the tumor microenvironment and patient anti-tumor immune response such as AMC, NLR, and PLR in conjunction with the clinical and laboratory parameters in MCL. The findings of this study prove that the clinical behavior and results of the disease both exhibit significant differences between the groups with low and high AMC, NLR, and PLR values at the time of diagnosis. Previous studies have shown that NLR has predictive value in the determination of mortality in hematologic malignancies such as DLBCL,[17] FL,[16] Hodgkin Lymphoma (HL)[24] and Multiple Myeloma.[25] This is the first study to investigate the prognostic importance of NLR in MCL. The study

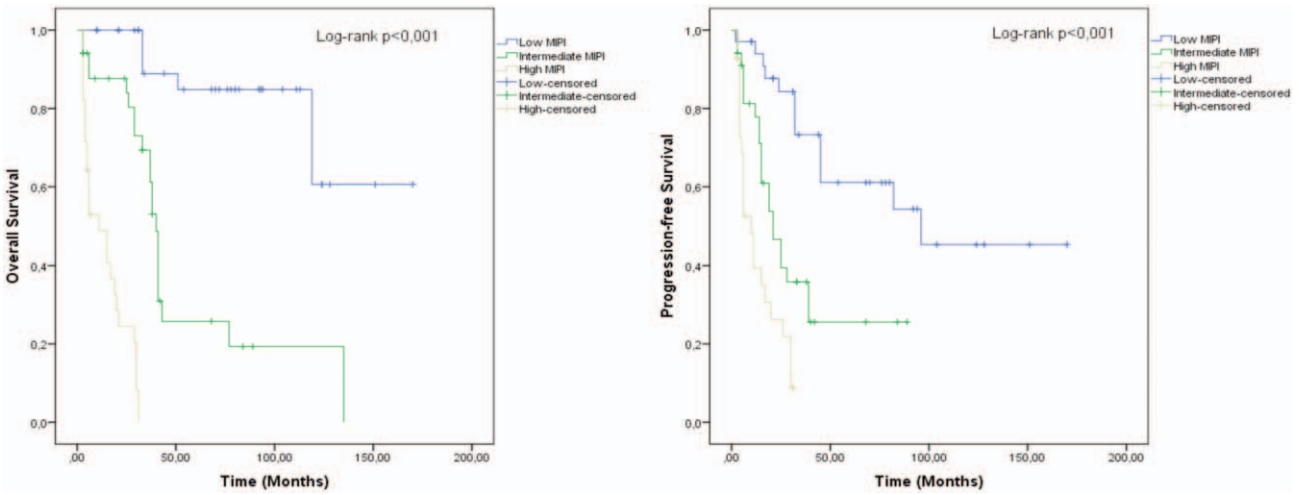

Figure 4. Comparison of survival rates according to MIPI. (A) MIPI OS graph (B) MIPI PFS graph MIPI = Mantle cell lymphoma International Prognostic Index, OS = overall survival, PFS = progression free survival.

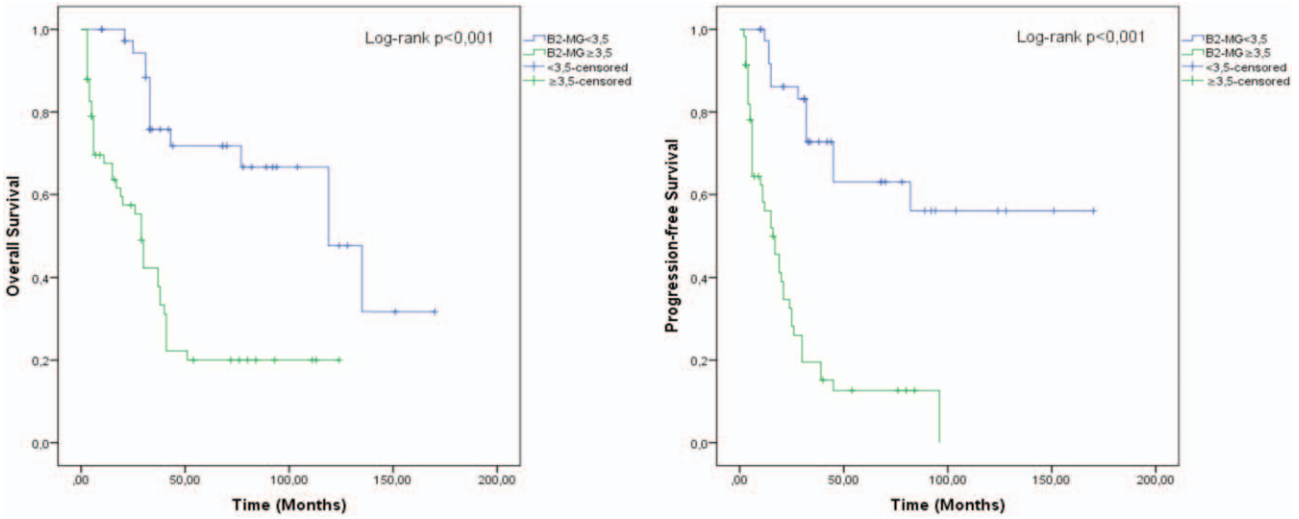

Figure 5. Comparison of survival rates according to B2-MG. (A) B2-MG OS graph (B) B2-MG PFS graph. B2-MG = beta-2 microglobulin, OS = overall survival, PFS = progression free survival.

has shown that NLR plays an important role in the progression of the disease; however, it was not found to be an independent risk factor for PFS and OS in the multivariate analysis. AMC, a component of the tumor microenvironment, has been shown to be a reliable prognostic factor in DLBCL,[18] and FL.[19] However; several immunologic studies on solid tumors have been conducted in recent years, wherein it was shown that monocytes that were elevated in the tumor microenvironment were actually CD14, CD45, and HLA-DR positive myeloid-derived suppressor cells (MDSCs).[14,15] MDSCs are a subgroup of immunosuppressive cells, and they identify a heterogenous group of cell population, i.e. granulocytic or monocytic, depending on their phenotypic properties. MDSCs have an immunosuppressive function and play an important role in cancer tolerance, wherein they also stimulate angiogenesis and play a role in tumor invasion and metastasis.[26] However, the number of studies on the role of this group of cells in NHL is limited.[27] AMC was first defined in MCL by Hoster et al. According to the study, high AMC was associated with poor clinical parameters but it was not included in the multivariate analysis.[9] The actual prognostic significance of AMC in MCL was the first demonstrated by Von Hohenstaufen et al. It was reported that by combining AMC and B2-MG with MIPI, it could provide a stronger prognostic risk classification.[20] The relationship between AMC and MCL was then evaluated in a limited number of studies and the prognostic value of AMC has been demonstrated.[21,22] In the study of Goy et al, ALC and AMC were used in combination instead of AMC. The authors investigated prognostic value of the postinduction therapy ALC/AMC in MCL prognosis. The results of the study conducted that postinduction therapy ALC/AMC ≥ 2 was associated with better 5-year OS. Also, patients with similar ALC/AMC ratio were found to be more tendency to have higher 5-year survival rates compared to the patients with high risk MIPI.[28] In another

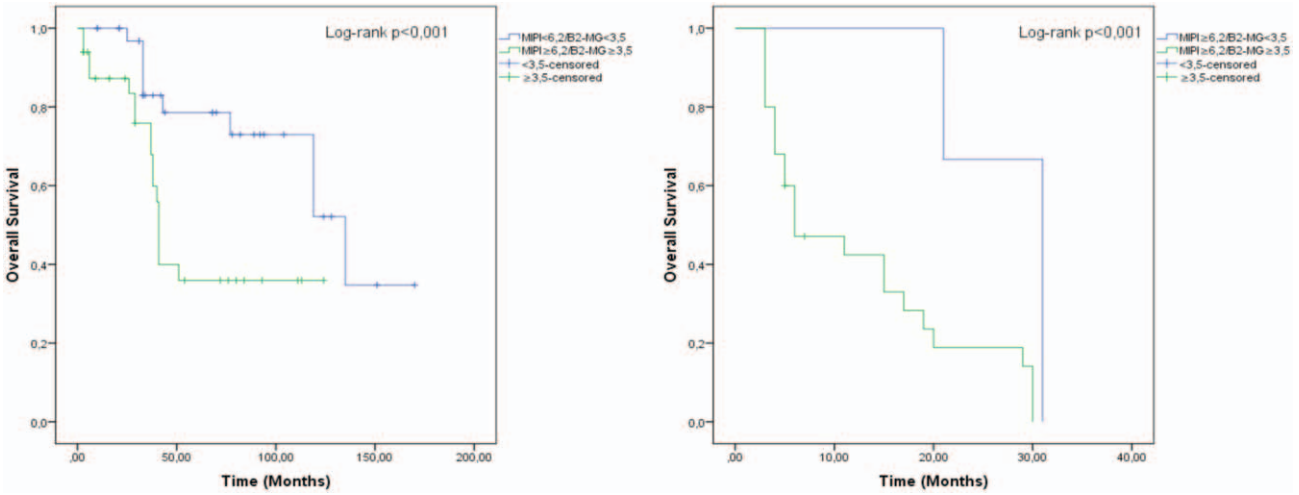

Figure 6. Comparison of OS rates according to MIPI and B2-MG. (A) B2-MG < 3.5 vs B2-MG ≥ 3.5 OS in MIPI low/intermediate risk group. (B) B2-MG < 3.5 vs B2-MG ≥ 3.5 OS in MIPI high risk group. OS = overall survival, MIPI = Mantle cell lymphoma International Prognostic Index, B2-MG = beta-2 microglobulin.

study, the relationship between AMC and survival was not observed.[23] The fact that studies in the literature provided different results could be associated with specifying the AMC cut-off value with median values in some studies and determining the same value using ROC analysis in others, which limits the predictive value of AMC. In this study, the AMC cut-off value was determined as 580×10^9/L using ROC analysis. Seventeen patients (34%) among 50 patients included in the group with AMC (<580) had progression following first-line treatment and a total of 20 patients (40%) died due to disease-related causes. In the group with AMC ≥ 580, 24 (52%) patients had progression following first-line treatment and a total of 33 patients (71%) died due to cancer-related causes. A high AMC value at the time of diagnosis was found to have a significant effect on disease progression ($P = .001$) but it had a poor correlation with OS. Increased progression and mortality rate seen in the group of patients with high AMC values implies resistance to chemotherapeutic agents. Previous studies suggested that AMC could be associated with resistance to chemotherapeutic agents in NHL.[29] The fact that statistical significance could not be attained for OS suggests that this condition could be related to the patient groups included in the study. Excluding the patients who had the blastoid type and nonhomogeneity of the chemotherapeutic agents administered in the first-line treatment are the limitations of this study.

Another investigated parameter associated with peripheral blood inflammatory cells in different cancer populations is PLR. Progression of tumor tissue depends on the formation of new blood vessels that provide oxygen and food for the tumor. Platelets play a role in tumor angiogenesis by secreting Vascular Endothelial Growth Factor (VEGF). Moreover, platelet activation protects the tumor cells from Natural killer cell (NK) activity. Platelet-derived lysophosphatidic acid increases metastatic activity, and therefore progression.[30] The prognostic significance of PLR on PFS and OS was demonstrated in DLBCL.[31] In another study conducted on patients with NK/T cell lymphoma, PLR was described as an independent risk factor for survival.[32] Another study on gastric DLBCL patients, it was found that PLR was associated with inferior PFS but it could not be described as an independent risk factor for PFS and OS.[17] Similar to the results of the study by Zhao et al, this study showed that a high PLR value was an important risk factor for disease progression and associated with inferior PFS; however, it could not be described as an independent risk factor. As far as could be determined, this study is the first study that investigates the prognostic value of PLR in MCL and a significant relationship was not observed between PLR and overall survival.

B2-MG is a human leukocyte antigen-class I molecule which is expressed in the cell membrane. B2-MG is a growth factor for the tumor and it plays a role in the proliferation, apoptosis inhibition and metastasis of the tumor.[33] Several studies have shown that B2-MG could be a useful prognostic factor in MCL.[12,20] This study also showed that an elevated B2-MG level was a poor prognostic factor in MCL. In order to ensure applicability, the B2-MG cut-off value was accepted as the upper limit of the local laboratory (B2-MG < 3.5 vs ≥3.5). Another parameter that was determined to be an independent risk factor in this study was the MIPI risk classification system. A high MIPI was associated with poorer PFS and poorer OS ($P = .002$, $P = .001$, respectively). In the following part of this study, the combined use of two parameters that were found to be poor prognostic factors, in the determination of PFS and OS were evaluated and the predictive value of MIPI was analyzed. Patients in the MIPI low/intermediate risk group with B2-MG ≥ 3.5 had poorer 5-year OS (5-year OS 48.5% vs 71.4%; $P < .001$) as compared to the patients in the MIPI low/intermediate risk group with B2-MG < 3.5. Patients in the MIPI high risk group with B2-MG ≥ 3.5 had significantly poorer OS as compared to the patients in the MIPI high risk group with B2-MG < 3.5 ($P < .001$).

The most important indicator in the management of MCL patients is the selection of the correct treatment according to age. Although MIPI is an important prognostic index, it does not provide sufficient information concerning a clinical course. Despite the developments in MCL treatment, it still remains to be an incurable disease with a poor prognosis. The improvement of disease outcome depends on administering a personalized risk-adaptive treatment. A risk-adaptive treatment requires defining a more sensitive risk classification system. Findings of this study indicate that the combined use of pretreatment serum B2-MG level and MIPI could provide a stronger risk classification system and enhance the prognostic value of MIPI.

Consequently, this study suggests that the AMC, NLR, and PLR are inexpensive tools that are useful for predicting progression in MCL, and also developing a new model prognostic index by combining MIPI with B2-MG, which plays a role in tumor development and progression, could guide the determination of high risk groups among patients and the selection of personalized risk-adaptive treatment.

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References

[1] Zhou Y, Wang H, Fang W, et al. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer 2008;113:791–8.
[2] Abrahamsson A, Albertsson-Lindblad A, Brown PN, et al. Real world data on primary treatment for mantle cell lymphoma: a Nordic Lymphoma Group observational study. Blood 2014;124:1288–95.
[3] Martin P, Chadburn A, Christos P, et al. Outcome of deferred initial therapy in mantle-cell lymphoma. J Clin Oncol 2009;27:1209–13.
[4] Rosenwald A, Wright G, Wiestner A, et al. The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in mantle cell lymphoma. Cancer Cell 2003;3:185–97.
[5] Nygren L, Baumgartner Wennerholm S, Klimkowska M, et al. Prognostic role of SOX11 in a population-based cohort of mantle cell lymphoma. Blood 2012;119:4215–23.
[6] Aukema SM, Hoster E, Rosenwald A, et al. Expression of TP53 is associated with the outcome of MCL independent of MIPI and Ki-67 in trials of the European MCL Network. Blood 2018;131:417–20.
[7] Choe JY, Yun JY, Na HY, et al. MYC overexpression correlates with MYC amplification or translocation, and is associated with poor prognosis in mantle cell lymphoma. Histopathology 2016;68:442–9.

[8] Navarro A, Clot G, Royo C, et al. Molecular subsets of mantle cell lymphoma defined by the IGHV mutational status and SOX11expression have distinct biologic and clinical features. Cancer Res 2012;72:5307–16.
[9] Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced- stage mantle cell lymphoma. Blood 2008;111:558–65.
[10] Wada N, Zaki MA, Hori Y, et al. Tumour-associated macrophages in diffuse large B-cell lymphoma: a study of the Osaka Lymphoma Study Group. Histopathology 2012;60:313–9.
[11] Nam SJ, Go H, Paik JH, et al. An increase of M2 macrophages predicts poor prognosis in patients with diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. Leuk Lymphoma 2014;55:2466–76.
[12] Yoo C, Yoon DH, Kim S, et al. Serum beta-2 microglobulin as a prognostic biomarker in patients with mantle cell lymphoma. Hematol Oncol 2016;34:22–7.
[13] Chihara D, Asano N, Ohmachi K, et al. Prognostic model for mantle cell lymphoma in the rituximab era: a nationwide study in Japan. Br J Haematol 2015;170:657–68.
[14] Mantovani A, Schioppa T, Porta C, et al. Role of tumor- associated macrophages in tumor progression and invasion. Cancer Metastasis Rev 2006;25:315–22.
[15] Murdoch C, Muthana M, Coffelt SB, et al. The role of myeloid cells in the promotion of tumour angiogenesis. Nat Rev Cancer 2008;8:618–61.
[16] Lee SF, Luque-Fernandez MA. Prognostic value of lymphocyte-to-monocyte ratio and neutrophil- to-lymphocyte ratio in follicular lymphoma: a retrospective cohort study. BMJ Open 2017;7:e017904.
[17] Zhao P, Zang L, Zhang X, et al. The lymphocyte-monocyte ratio and the platelet-lymphocyte ratio at diagnosis as independent prognostic factors in primary gastrointestinal diffuse large B cell lymphoma. Indian J Hematol Blood Transfus 2017;33:333–41.
[18] Wilcox RA, Ristow K, Habermann TM, et al. The absolute monocyte and lymphocyte prognostic score predicts survival and identifies high-risk patients in diffuse large-B-cell lymphoma. Leukemia 2011;25:1502–9.
[19] Wilcox RA, Ristow K, Habermann TM, et al. The absolute monocyte count is associated with overall survival in patients newly diagnosed with follicular lymphoma. Leuk Lymphoma 2012;53:575–80.
[20] von Hohenstaufen KA, Conconi A, de Campos CP, et al. Prognostic impact of monocyte count at presentation in mantle cell lymphoma. Br J Haematol 2013;162:465–73.
[21] Koh YW, Shin SJ, Park C, et al. Absolute monocyte count predicts overall survival in mantle cell lymphomas: correlation with tumour-associated macrophages. Hematol Oncol 2014;32:178–86.
[22] Chen XP, Zhao Y, Wang QS, et al. Clinical Characteristics and Prognosis of 34 Patients with Mantle Cell Lymphoma: a retrospective analysis. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2015;23:1601–6.
[23] George A, Prince HM, Szer J, et al. Prognostic impact of monocyte count at presentation in mantle cell lymphoma. Br J Haematol 2014;164: 890–3.
[24] Reddy JP, Hernandez M, Gunther JR, et al. Pre-treatment neutrophil/lymphocyte ratio and platelet/lymphocyte ratio are prognostic of progression in early stage classical Hodgkin lymphoma. Br J Haematol 2018;180:545–9.
[25] Zeng Q, Liu Z, Li Q, et al. Prognostic value of neutrophil to lymphocyte ratio and clinicopathological characteristics for multiple myeloma: A meta-analysis. Medicine (Baltimore) 2018;97:e12678.
[26] Serafini P, Borrello I, Bronte V. Myeloid suppressor cells in cancer: recruitment, phenotype, properties, and mechanisms of immune suppression. Semin Cancer Biol 2006;16:53–65.
[27] Lin Y, Gustafson MP, Bulur PA, et al. Immunosuppressive CD14 + HLA-DRlow/monocytes in B-cell non-Hodgkin lymphoma. Blood 2011;117: 872–81.
[28] Goy A, Feldman T, Leslie LA, et al. Prognostic value of the absolute lymphocyte to monocyte (ALC/AMC) ratio on overall survival among patients with mantle cell lymphoma. J Clin Oncol 2017;35: (suppl; abstr e19030).
[29] Wilcox RA, Wada DA, Ziesmer SC, et al. Monocytes promote tumor cell survival in T-cell lymphoproliferative disorders and are impaired in their ability to differentiate into mature dendritic cells. Blood 2009;114: 2936–44.
[30] Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011;11:123–34.
[31] Zhao P, Zang L, Zhang X, et al. Novel prognostic scoring system for diffuse large B-cell lymphoma. Oncol Lett 2018;15:5325–32.
[32] Wang KF, Chang BY, Chen XQ, et al. A prognostic model based on pretreatment platelet lymphocyte ratio for stage IE/IIE upper aerodigestive tract extranodal NK/T cell lymphoma, nasal type. Med Oncol 2014;31:318.
[33] Huang WC, Havel JJ, Zhau HE, et al. Beta2-microglobulin signaling blockade inhibited androgen receptor axis and caused apoptosis in human prostate cancer cells. Clin Cancer Res 2008;14:5341–7.