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Negative prognostic impact of low absolute CD4+ T cell counts in peripheral blood in mantle cell lymphoma

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Key words

$CD4^+$ T cell, mantle cell lymphoma, overall survival, prognosis, T-cell subsets

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Tumor microenvironment and host immunity are closely related to outcome in patients with mantle cell lymphoma (MCL). However, few researchers have focused on the prognostic value of peripheral blood lymphocyte subsets counts. The purpose of this study was to investigate the prognostic value of lymphocyte subsets and absolute monocyte counts. Sixty-eight patients were analyzed retrospectively. Absolute $CD4^+$ T cell counts (ACD4C), $CD8^+$ T cell counts, nature killer cell counts, and CD4/CD8 ratios were assessed by peripheral blood flow cytometry and correlated with clinical parameters and long-term outcomes. The median follow-up for all patients was 21 months and the median survival time was 44 months. The overall survival (OS) rate at 1, 3, and 5 years was 80%, 51%, and 41%, respectively. In our cohort, high absolute monocyte count, and low ACD4C and CD4/CD8 ratio were associated with unfavorable OS ($P = 0.029$, $P = 0.027$, and $P = 0.045$, respectively) by univariate analysis. Multivariate analysis indicated that low ACD4C was a significant predictor of unfavorable OS ($P = 0.004$) independent of the simplified MCL International Prognostic Index ($P = 0.048$) in patients treated with or without rituximab ($P = 0.011$). Low $CD4^+$ T cell counts proved to be a significant predictor of unfavorable OS in patients with MCL.

Mantle cell lymphoma (MCL) is an uncommon subtype of non-Hodgkin's lymphoma, comprising 3–6% of all non-Hodgkin's lymphomas. The majority of patients have a cytogenetic hallmark of chromosomal translocation t(11;14) causing the overexpression of cyclin D1 and deregulation of the cell cycle.[1,2] The clinical course of MCL is heterogeneous with median overall survival (OS) of 3–5 years. In spite of the chemosensitive nature of MCL, the majority of patients who respond to therapy initially will eventually relapse, even though some patients may have an indolent progress and do not need treatment immediately. Given this heterogeneity and the limited discriminatory power of the International Prognostic Index (IPI), the simplified MCL IPI (sMIPI) including age, performance status, white blood cell counts, and lactate dehydrogenase (LDH) level enables assessment of the prognosis of individual patients. As sMIPI was developed from patients with advanced stage disease in the pre-rituximab era,[3] and the variables of sMIPI were just a reflection of tumor burden and serve as indirect markers for the biological characteristics of MCL, many other prognostic factors were analyzed such as Ki-67, TP53, stage, serum β2-microglobulin, chromosome karyotype, and other parameters.[1,3,4] Unfortunately, little research into MCL took the host immunity and tumor microenvironment into account. More and more evidence has proved the interaction among lymphoma cells, stromal cells, and immune cells. Monocytes/macrophages can promote angiogenesis, suppress antitumor immunity, and drive the survival of lymphoma cells.[5] $CD4^+$ and $CD8^+$ T cells, and natural killer (NK) cells as immune cells play a central role in inducing immune responses against tumor. Nygren *et al.*[6] found that the counts of $CD3^+$, $CD4^+$, and $CD8^+$ T lymphocytes in MCL nodes were higher in indolent MCL. Higher peritumoral $CD4^+$ T cell count and CD4/CD8 ratio correlated with longer OS. However, there has been no research into the prognostic value of peripheral blood T lymphocyte subset counts in MCL.

The present study aimed to evaluate the prognostic relevance of absolute monocyte counts (AMC), $CD4^+$ T cell counts (ACD4C), $CD8^+$ T cell counts (ACD8C), NK cell counts

(ANKC), and CD4/CD8 ratio in MCL compared to the conventional prognostic markers including age, Eastern Cooperative Oncology Group score, clinical staging, sMIPI, LDH, B symptoms, and the use of rituximab or not.

Materials and Methods

Patients. A total of 68 consecutive histologically proven cases of MCL were included from December 2006 to December 2015 at the First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital (Nanjing, China). This study was approved by Institutional Review Boards of our hospital. Diagnosis of MCL was based on the 2008 WHO Classification, and detection of cyclin D1 overexpression by immunohistochemistry or t(11;14) translocation by FISH was mandatory.[7] Initial evaluation included complete blood count, blood chemistry, bone marrow aspiration and biopsy, contrast-enhanced computed tomography of neck, chest abdomen, and pelvis, or 18F-fluorodeoxyglucose positron emission tomography/computed tomography of whole body imaging results. Baseline clinical characteristics were available for all patients, including age, gender, Eastern Cooperative Oncology Group score, bone marrow involvement (BMI), Ann Arbor stage, B symptoms, white blood cell count, LDH, and serum β2-microglobulin. The response was assessed during and after the treatment or disease progression was suspected. Peripheral blood flow cytometry was available in 66 patients, and the lymphocyte subset counts calculated from the percentages obtained by flow cytometry; ACD4C refers to $CD3^+CD4^+$ lymphocyte counts of blood, ACD8C to $CD3^+CD8^+$ lymphocyte counts, and ANKC to $CD16^+CD56^+$ lymphocyte counts.

Flow cytometric analysis. The frequencies of $CD3^+CD4^+$ T cells, $CD3^+CD8^+$ T cells, and $CD16^+CD56^+$ lymphocytes were determined by a FACSCalibur flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). The following murine anti-human mAbs were used: anti-CD3-FITC, anti-CD4-phycoerythrin, anti-CD8-allophycocyanin, anti-CD16-phycoerythrin, and anti-CD56-allophycocyanin. All of these antibodies were provided by BD Biosciences (San Jose, CA, USA). Lymphocytes were delineated by forward scatter/side scatter dot plots and CellQuest software (BD Biosciences) was used to analyze data.

Statistical analysis. The OS was defined as the time between diagnosis and death as a result of any cause or last follow-up. The optimal cut-offs of AMC, ACD4C, ACD8C, ANKC, and CD4/CD8 ratio were selected using receiver–operator characteristic (ROC) curve analysis according to OS. The Kaplan–Meier method was used to estimate OS, and the survival curves were compared by log–rank test. The Cox proportional hazards models was used for the estimation of hazard radio and its confidence interval in both univariate and multivariate analysis. The Mann–Whitney *U*-test was used to compare median lymphocyte subset counts as well as AMC among subgroups. All statistical analyses were carried out using SPSS for Windows (version 20.0; IBM, Armonk, NY, USA) and GraphPad Prism 6 (GraphPad Software, San Diego, CA), and all tests were two-sides with 5% defined as level of significant.

Results

Patient characteristics. Clinical characteristics of all patients ($n = 68$) at admission are summarized in Table 1. The patient group included 56 men and 12 women with an age range of 28–81 years (median, 60.5 years); 50% of them were more than 60 years old. Most patients (94.1%) had advanced stage (Ann Arbor stage, III–IV) and 76.5% had BMI. B symptoms were seen in 60.3% of the patients. Twenty-seven (39.7%) had elevated LDH. The intermediate- to high-risk patients according to sMIPI score comprised 63.3% of the total group. The median ACD4C, ACD8C, ANKC, CD4/CD8 ratio, and AMC were 0.45×10^9/L (range, 0.03–2.96), 0.43×10^9/L (range, 0.04–3.43), 0.24×10^9/L (range, 0.02–4.03), 1.03 (range, 0.08–12.00), and 0.50×10^9/L (range, 0.02–10.26), respectively. The median follow-up was 21 months (range, 6–87 months) and the median OS of all cases was 44 months. The 1-, 3-, and 5-year OS was 80%, 51%, and 41%, respectively.

Table 1. Clinical characteristics of 68 patients with mantle cell lymphoma

Characteristic	Patients, *n* (%)
Gender, male	56 (82.4)
Age >60 years	34 (50.0)
ECOG PS ≥2	16 (23.5)
B symptoms present	41 (60.3)
BMI present	52 (76.5)
LDH >NUV	27 (39.7)
Ann Arbor stage	
I–II	4 (5.9)
III–IV	64 (94.1)
sMIPI	
Low risk	25 (36.8)
Intermediate risk	21 (30.9)
High risk	22 (32.4)
Chemotherapy	
Including rituximab	51 (75.0)
Not including rituximab	17 (25.0)
WBC >NUV	24 (35.3)
β2-MG >NUV	50 (82.0)
	Median (range)
AMC, $\times 10^9$/L	0.50 (0.02–10.26)
ACD4C, $\times 10^9$/L	0.45 (0.03–2.96)
ACD8C, $\times 10^9$/L	0.43 (0.04–3.43)
CD4/CD8 ratio	1.03 (0.08–12.00)
ANKC, $\times 10^9$/L	0.24 (0.02–4.03)

β2-MG, serum β2-microglobulin level; ACD4C, absolute $CD3^+CD4^+$ T lymphocyte count; ACD8C, absolute $CD3^+CD8^+$ T lymphocyte count; AMC, absolute monocyte count; ANKC, absolute $CD16^+CD56^+$ natural killer cell count; BMI, bone marrow involvement; ECOG, Eastern Cooperative Oncology Group; LDH, serum lactate dehydrogenase; NUV, normal upper value; PS, performance status; sMIPI, simplified mantle cell lymphoma International Prognostic Index; WBC, white blood cells.

Treatment at diagnosis. Patients younger than 45 years were treated with the hyper-CVAD regimen (cyclophosphamide, doxorubicin, vincristine, and dexamethasone) alternated with the MA regimen (high-dose methotrexate and cytarabine). Patients aged between 45 and 70 years were treated with a modified hyper-CVAD regimen. Patients aged >70 years were treated with CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisolone)-like regimens. Fifty-one (75%) cases were treated with rituximab-containing therapy, 17 (25%) cases with chemotherapy.

Association between AMC, lymphocyte counts, and clinical features. The distribution of lymphocyte subsets counts is shown in Table 2. While analyzing ACD4C and ACD8C, we found no association between ACD4C or ACD8C and clinical features. Patients with lower ANKC had more advanced sMIPI score ($P = 0.003$) and more BMI ($P = 0.05$). High AMC was more likely in men ($P = 0.016$). There was no significant association between CD4/CD8 ratio and clinical features.

Association between AMC, lymphocyte subset counts, and survival. As there are no standard cut-off points available for

Table 2. Differences in absolute monocyte counts (AMC), absolute $CD3^+CD4^+$ T lymphocyte counts (ACD4C), absolute $CD3^+CD8^+$ T lymphocyte counts (ACD8C), absolute $CD16^+CD56^+$ natural killer cell counts (ANKC), and CD4/CD8 ratios in patients with mantle cell lymphoma

Characteristics	Median AMC (range), $\times 10^9$/L		*P*-value	Median ACD4C (range), $\times 10^9$/L		*P*-value	Median ACD8C (range), $\times 10^9$/L		*P*-value	Median ANKC (range), $\times 10^9$/L		*P*-value	Median CD4/CD8 ratio (range)		*P*-value
Sex															
Male	0.55	0.02–10.26	**0.02**	0.46	0.07–1.88	0.36	0.46	0.04–2.00	0.59	0.25	0.02–3.75	0.540	1.10	0.08–12.00	0.21
Female	0.37	0.11–2.60		0.28	0.03–2.96		0.37	0.12–3.43		0.20	0.06–4.03		0.86	0.22–2.86	
Age, years															
≤60	0.51	0.03–2.60	0.63	0.48	0.03–2.96	0.76	0.41	0.04–3.43	0.32	0.21	0.02–2.55	0.320	1.16	0.22–4.96	0.48
>60	0.50	0.02–10.26		0.44	0.16–1.88		0.48	0.10–2.00		0.25	0.03–4.03		0.92	0.08–12	
ECOG PS															
0–1	0.50	0.02–10.26	0.91	0.45	0.03–2.96	0.63	0.48	0.04–3.43	0.37	0.23	0.02–4.03	0.560	1.03	0.08–12.00	0.95
≥2	0.50	0.10–5.46		0.46	0.11–1.05		0.32	0.19–1.12		0.25	0.05–3.75		1.05	0.28–2.40	
B symptoms															
Yes	0.55	0.02–10.26	0.21	0.46	0.11–2.96	0.77	0.53	0.10–3.43	0.17	0.26	0.03–4.03	0.410	0.89	0.08–4.96	0.12
No	0.43	0.04–3.10		0.46	0.03–1.71		0.39	0.04–1.73		0.21	0.02–1.42		1.20	0.22–12.00	
Ann Arbor stage															
I–II	0.49	0.48–0.70	0.90	0.68	0.37–0.96	0.39	0.55	0.25–1.73	0.62	0.14	0.03–0.16	0.060	1.31	0.25–3.10	0.62
III–IV	0.51	0.02–10.26		0.46	0.03–2.96		0.43	0.04–3.43		0.25	0.02–4.03		1.01	0.08–12.00	
sMIPI															
Low risk	0.5	0.19–1.28	0.15	0.45	0.03–1.04	0.12	0.39	0.12–2.00	0.32	0.16	0.02–2.55	**0.003**	1.17	0.08–0.96	0.61
Intermediate risk	0.43	0.03–2.60		0.41	0.07–2.96		0.37	0.04–3.43		0.18	0.07–1.90		0.89	0.25–3.15	
High risk	0.67	0.02–10.26		0.52	0.16–1.71		0.57	0.14–1.96		0.51	0.06–4.03		0.97	0.25–12.00	
BMI															
Yes	0.54	0.02–10.26	0.37	0.46	0.03–2.96	0.72	0.41	0.04–3.43	0.38	0.33	0.02–4.03	**0.050**	1.00	0.22–12.00	0.84
No	0.48	0.04–0.85		0.44	0.13–1.04		0.53	0.17–2.00		0.16	0.03–0.88		1.17	0.08–3.10	
LDH															
≤NUV	0.49	0.1–2.6	0.55	0.45	0.03–2.96	0.68	0.45	0.12–3.43	0.53	0.21	0.02–4.03	0.420	0.99	0.71–4.96	0.83
>NUV	0.55	0.02–10.26		0.47	0.07–1.71		0.43	0.04–1.96		0.26	0.05–3.75		1.17	0.25–12.00	
Chemotherapy															
Containing rituximab	0.49	0.02–10.26	0.48	0.44	0.11–2.96	0.54	0.41	0.14–3.43	0.47	0.24	0.02–4.03	0.840	1.07	0.08–12.00	0.54
Not containing rituximab	0.60	0.04–5.46		0.51	0.03–1.05		0.62	0.04–1.20		0.19	0.05–3.75		0.91	0.22–3.15	
β2-MG															
≤NUV	0.37	0.2–0.70	0.07	0.43	0.13–1.04	0.97	0.39	0.17–0.79	0.48	0.21	0.13–0.36	0.460	1.17	0.25–3.10	0.33
>NUV	0.54	0.02–10.26		0.44	0.03–2.96		0.47	0.04–3.43		0.25	0.03–4.03		1.01	0.08–12.00	

Bold values indicate significance ($P < 0.05$). β2-MG, β2-microglobulin; BMI, bone marrow involvement;ECOG, Eastern Cooperative Oncology Group; LDH, serum lactate dehydrogenase; NUV, normal upper value; PS, performance status; sMIPI, simplified mantle cell lymphoma International Prognostic Index.

AMC, ACD4C, ACD8C, ANKC, or CD4/CD8 ratio, we selected the cut-off values by maximal sensitivity and specificity of ROC curves according to OS. The cut-off values were: AMC, 0.8×10^9/L; ACD4C, 0.445×10^9/L; ACD8C, 0.325×10^9/L; ANKC, 0.32×10^9/L; and CD4/CD8 ratio, 0.635. We found that 48.5% (32/66), 40.9% (27/66), and 59.7% (37/62) of patients had low ACD4C, ACD8C, and ANKC and 26.5% (18/68) had high AMC. Low CD4/CD8 ratio was documented in 21.2% (14/66) cases in this series.

Analysis of ACD4C showed a significant difference between low and high ACD4C ($P = 0.027$) (Fig. 1). The 3-year OS rate of patients with high ACD4C was 70%, whereas that of patients with low ACD4C was 36%. No significant difference in OS was observed between patients with low and high ACD8C ($P = 0.25$). The 3-year OS rate of patients with high ACD8C was 59%; that of patients with low ACD8C was 42%. Analysis of CD4/CD8 ratio showed a significant difference in OS between patients with low and high ratio ($P = 0.045$) (Fig. 2). The 3-year OS among patients with high CD4/CD8 ratio was 60%, whereas that among patients with low CD4/CD8 ratio was 25%. Analysis of ANKC showed no significant difference in OS between patients with low and high ANKC ($P = 0.68$). The 3-year OS among patients with high ANKC was 61%, whereas that among patients with low ANKC was 56%. Analysis of AMC showed a significant difference between patients with low and high AMC ($P = 0.029$) (Fig. 3). The 3-year OS among patients with low AMC was 58%, whereas that among patients with high AMC was 30%.

Prognosis factors. The univariate analyses of OS are shown in Table 3. Because of the limited data, only four cases in our cohort had stage I/II disease and we did not analyze the influence of staging. Fifteen factors were included in the univariate analysis including five immune microenvironment factors and 10 non-immune microenvironment factors. Eight factors were significantly associated with OS, including B symptoms ($P = 0.01$), BMI ($P = 0.017$), sMIPI score ($P = 0.023$), not using rituximab ($P = 0.02$), LDH ($P < 0.001$), AMC ($P = 0.029$), ACD4C ($P = 0.027$), and CD4/CD8 ratio ($P = 0.045$). All factors with a significant P-value of <0.05 in the univariate analysis were then entered into multivariate analysis. By multivariate analysis, patients with high sMIPI score ($P = 0.048$), low ACD4C ($P = 0.004$), and not using rituximab ($P = 0.011$) were predicted to have unfavorable OS.

Discussion

The host immune system plays an extremely important role in the pathogenesis and progress of lymphoma. In addition to tumor elimination, the host immune reaction can initiate tumorigenesis through interaction with the microenvironment, such as extranodal marginal zone lymphoma.[8,9] The complex role of the microenvironment in both initiation and elimination of tumor has drawn considerable attention to lymphoma. Lymphopenia has been reported to be an adverse prognostic factor in some aggressive lymphomas.[10–12] However, in MCL, BMI is quite common.[13,14] Cancer cells account for the majority of total lymphocyte counts, so we chose T cell counts and NK cell counts as prognostic factors by flow cytometry in our study.

The main types of antitumor immune cells are CD4+ and CD8+ T cells and NK cells; many studies have reported changes in tumor-infiltrating lymphocytes in patients with different types of cancer.[15–17] Recently, a study compared the T cell subgroups in lymph node biopsy between MCL and reactive lymph nodes. In this study, higher levels of total T cells and CD8+ T cells, and especially CD4+ T cells, were associated with indolent disease and these cell counts decreased in a more aggressive histology. High CD4/CD8 ratio was associated with favorable OS independent of sMIPI and high p53 expression.[6] Nevertheless, no study has investigated the prognostic relevance of lymphocyte counts in peripheral blood in MCL patients. In our cohort, the ROC curve analysis showed that ACD4C <0.445×10^9/L, ACD8C <0.325×10^9/L, ANKC <0.32×10^9/L, and CD4/CD8 ratio <0.635 were the most discriminative cut-offs. The ACD4C and CD4/CD8 ratio had significant impact on OS by univariate analysis. However, only ACD4C <0.445×10^9/L was predictive of unfavorable prognosis in both univariate and multivariate analysis. The prognostic impact of CD4/CD8 ratio may be a reflection of the reduction of ACD4C.

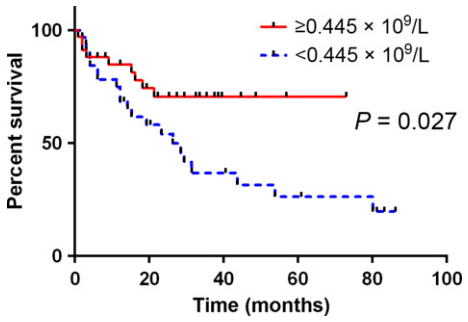

Fig. 1. Overall survival of 66 patients with mantle cell lymphoma according to absolute CD4+ T cell counts at time of diagnosis, by Kaplan–Meier estimation.

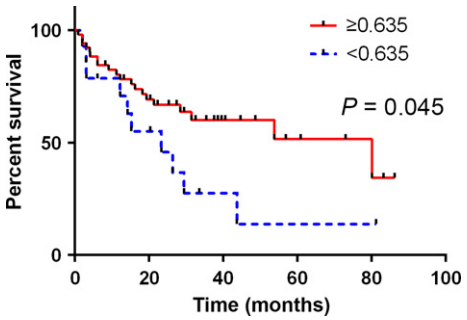

Fig. 2. Overall survival of 66 patients with mantle cell lymphoma according to CD4/CD8 ratio at time of diagnosis, by Kaplan–Meier estimation.

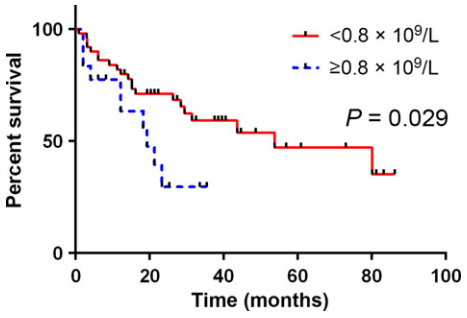

Fig. 3. Overall survival of 68 patients with mantle cell lymphoma according to absolute monocyte counts at time of diagnosis, by Kaplan–Meier estimation.

Table 3. Univariate and multivariate analysis of overall survival in 68 patients with mantle cell lymphoma

Variable	Univariate analysis			Multivariate analysis		
	P-value	HR	95% CI	*P*-value	HR	95% CI
Sex, female	0.388	0.63	0.22–1.81	ND	ND	ND
Age >60 years	0.811	1.09	0.54–2.22	ND	ND	ND
ECOG PS ≥2	0.110	1.93	0.85–4.40	ND	ND	ND
B symptoms, yes	**0.010**	2.79	1.24–6.30	0.171	1.980	0.74–5.29
sMIPI	**0.023**	1.87	1.18–2.98	**0.048**	2.050	1.01–4.17
BMI, yes	**0.017**	3.45	1.18–10.14	0.201	2.200	0.66–7.42
Chemotherapy without rituximab	**0.020**	2.42	1.12–5.22	**0.011**	3.450	1.33–8.97
WBC >NUV	0.068	1.96	0.94–4.09	ND	ND	ND
AMC >0.8 × 10^9/L	**0.029**	2.33	1.06–5.11	0.381	1.490	0.61–3.60
LDH >NUV	**<0.001**	4.16	1.94–8.89	0.210	1.730	0.74–4.07
β2-MG >NUV	0.057	3.66	0.87–15.44	ND	ND	ND
ACD4C <0.445 × 10^9/L	**0.027**	2.37	1.08–5.23	**0.004**	5.232	1.70–16.07
ACD8C <0.325 × 10^9/L	0.253	1.52	0.74–3.12	ND	ND	ND
CD4/CD8 ratio <0.635	**0.045**	2.13	0.99–4.57	0.411	1.440	0.61–3.42
ANKC <0.32 × 10^9/L	0.679	1.19	0.51–2.78	ND	ND	ND

Bold values indicate significance ($P < 0.05$). All factors with a significant *P*-value in the univariate analysis underwent multivariate analysis. β2-MG, β2-microglobulin; ACD4C, absolute $CD3^+CD4^+$ T lymphocyte count; ACD8C, absolute $CD3^+CD8^+$ T lymphocyte count; AMC, absolute monocyte count; ANKC, absolute $CD16^+CD56^+$ natural killer cell count; BMI, bone marrow involvement; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, serum lactate dehydrogenase; ND, not done; NUV, normal upper value; PS, performance status; sMIPI, simplified mantle cell lymphoma International Prognostic Index; WBC, white blood cells.

The immune function of cancer patients is abnormal, and the number and function of $CD4^+$ T lymphocytes was also altered in patients with MCL. However, the significant difference in prognosis between patients with high and low ACD4C indicated that $CD4^+$ T lymphocytes remain part of the antitumor function. Higher ACD4C indicates more efficient antitumor function and prolonged survival. Chen *et al.*[18] showed that ACD4C and ACD8C decreased more significantly in cancer patients than in normal controls especially in advanced stage of disease. Rakhra *et al.*[19] found $CD4^+$ T cells were specially required to shut down the angiogenesis and induce cell senescence for tumor regression on oncogene inactivation. They also hypothesized that $CD4^+$ T cells can enhance the efficacy of therapeutic agents, and the combination of immunotherapy and targeted therapy might be a particularly effective antitumor treatment. We suspected that MCL cells could decrease the number and suppress the function of immune cells. Wang *et al.*[20] proved that MCL cells can inhibit T cell proliferation and are resistant to T cell-mediated cytolysis through B7–H1 interaction. In addition, blocking B7–H1 interaction can prime more $CD4^+$ or $CD8^+$ memory effector T cells.

Elevated circulating AMC was an inferior prognostic factor in several lymphoma subsets including MCL.[21,22] Monocytes can be recruited to tumor sites and differentiated into tumor-associated macrophages. Tumor-associated macrophages and monocytes can promote tumor progression by stimulating proliferation and angiogenesis.[23,24] In our study, we found a survival difference between low and high AMC, but the prognostic value of AMC was not maintained in the multivariate analysis, which was probably due to the small sample size of this study, short follow-up time, or different cut-offs.

In summary, our results suggest that the baseline ACD4C level may be a potent prognostic factor in MCL patients. A decreased ACD4C level was associated with inferior OS independent of sMIPI and chemotherapy with or without rituximab in multivariate analysis. Therefore, ACD4C might be a useful factor for risk stratification and treatment decisions. Further prospective studies with large patient cohorts are needed to validate the prognostic value of ACD4C in MCL.

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Disclosure Statement

The authors have no conflict of interest.

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