Complement 4 Aids in the Prediction of Newly Diagnosed Multiple Myeloma Outcome in Patients

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ABSTRACT

BACKGROUND: A cure for the heterogeneous hematological malignancy multiple myeloma (MM) is yet to be developed. To date, the early risk factors associated with poor outcomes in MM have not been fully elucidated. Studies have shown an aberrant complement system in patients with MM, but the precise association necessitates elucidation. Therefore, this study scrutinizes the correlation between serum complement level and the disease outcome of patients with MM.

METHODS: A retrospective analysis of 72 patients with MM (new diagnosis) with complement C4 and C3 along with common laboratory indicators was done. The Pearson χ^2 test and the Mann-Whitney *U*-test were done to evaluate categorical or binary variables and intergroup variance, respectively. Kaplan-Meier test and Cox proportional hazards regression were used for quantification of overall survival (OS) and univariate or multivariate analyses, respectively.

RESULTS: The Cox proportional hazard model analysis unveiled the following: platelet $\leqslant 115.5 \times 10^9$/L (hazard ratio [HR] = 5.82, 95% confidence interval [CI] = 2.522-13.436, $P < .001$), complement C4 $\leqslant 0.095$ g/L(HR = 3.642, 95% CI = 1.486-8.924, $P = .005$), age $\geqslant 67$ years (HR = 0.191, 95% CI = 0.078-0.47, $P < .001$), and bone marrow plasma cell percentage $\geqslant 30.75\%$ (HR = 0.171, 95% CI = 0.06-0.482, $P = .001$) can be used as independent predictors of OS. Of these, advanced age, low platelet level, and a high proportion of bone marrow plasma cells have been implicated in poor outcomes in patients with MM. Interestingly, a low complement 4 level can function as a new indicator of poor prognosis in patients with MM.

CONCLUSION: Low levels of C4 are indicative of a poor outcome in newly diagnosed patients with MM.

KEYWORDS: Multiple myeloma, complement C4, outcome, prognosis, risk factors

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Introduction

Multiple myeloma (MM) is a heterogeneous hematologic malignancy, most of which remains incurable. The median survival of patients with MM is just about 5 years, during which the disease may be pronounced.[1] Currently, the therapy is selected depending on the stage of disease progression and the risk of poor prognosis. This warrants risk stratification at diagnosis to help us judge the prognosis for modifying the therapy. Nowadays, the primary methods used to stage patients with MM at diagnosis are the Durie-Salmon Staging System (DS),[2] International Staging System (ISS),[3] and Revised International Staging System (R-ISS).[4] Although many adverse risk factors have been identified, including advanced age, low platelet (PLT), low hemoglobin (Hgb), high bone marrow plasma cell (BPC) proportion, and hypercalcemia,[5-8] the heterogeneity of the malady lacks a lucid clarification. Prognostic indicators for myeloma are constantly being updated as the disease, new treatments, and new technologies evolve. For example, high levels of interleukin (IL)-6 and IL-17A may also able to predict poor prognosis in patients with MM.[9]

The hematologic system situated in the immune microenvironment is involved to plausibly interact with immune cells, local antibodies, or the complement system. This accounts for the aberrant specific complement component levels in patients with several hematological malignancies to impact complement activation or cascade to have a bearing on the prognosis of the disease. Michelis et al[10] found that patients with chronic lymphocytic leukemia have abnormal C5 patterns, that is,

increased levels of C5b-9 (SC5b-9) and C5a, which lead to impaired activation of the classical pathway and may impair response to immunotherapy. Moreover, studies have shown that variation in complement genes (such as MASP2, C5, and C9) is closely related to the development of non-Hodgkin lymphoma (NHL).[11] Variations in C9 and complement regulatory genes, for example, event-free survival (EFS) in follicular lymphoma (FL), display an association with CFHR5, Factor H, CD55, CD46, and CFHR1, whereas EFS for diffuse large B-cell lymphoma (DLBCL) is linked to C7 variants.[12]

Research has revealed the aberrant profile of the complement system as an integral part of the immune response in patients with MM. Zurlo et al[13] demonstrated aberrant serum complement deposition and composition in patients with myeloma, which was negatively correlated with monoclonal protein concentration, with no evident correlation with disease activity or infection. Lugassy et al[14] scrutinized the complement system of 22 patients with myeloma to unveil a deficiency of complement components in the classical pathway in almost all patients, but the alternative and terminal pathways were normal in most patients with myeloma. In addition, the defective binding effect of complement and *Streptococcus pneumoniae* in patients with MM possibly leads to an increased incidence of infections of this pathogen in these patients.[15]

To summarize, previous findings were suggestive of aberrations in the complement system in patients with MM, but the correlation between the complement system and prognosis of MM has not been adequately described. This led us to probe the main complement components, C4 and C3, in combination with other common laboratory test indicators, to elucidate the potential risk factors for patients with MM.

Methods

Patients

We retrospectively analyzed 72 newly diagnosed patients with MM at the Department of Hematology at the First People's Hospital of Yunnan Province between July 1, 2017, and January 1^{s}, 2019. Diagnosis of MM is in accordance with the International Myeloma Working Group criteria.[16] The enrolled patients were all clearly diagnosed with MM and only received chemotherapy. Patients who underwent hematopoietic stem cell transplantation after chemotherapy or who had other hematological diseases or other malignancies will be excluded. The follow-up time was 2 years. All patients' medical records, laboratory results, and clinical features were obtained at the time of diagnosis. Follow-up of the study was done by telephone or by checking medical records, and the results were recorded on the final follow-up day. The overall survival (OS) of patients from diagnosis of MM to the last follow-up or death during follow-up was calculated. Scoured clinical parameters included age, sex, percentage of BPC, ISS stage, light chain κ/λ, β2-microglobulin, complement C4, complement C3, C-reactive protein (CRP), Hgb, PLT, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), albumin, globulin, blood urea nitrogen (BUN), creatinine (Cr), uric acid (UA), activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), date of initial treatment, survival status, and date of death or last follow-up. Blood samples from all patients were obtained at the time of first admission and were taken before chemotherapy or any special treatment. This study received permission from the Ethics Committee of the First People's Hospital of Yunnan Province (KHLL2021-KY138) and was strictly conducted in accordance with the principles of the Declaration of Helsinki, the International Code of Ethics for Biomedical Research Involving Humans jointly formulated by the World Health Organization, and the Council of International Medical Science Organizations and federal regulations. All the individuals issued informed consent for examining their electronic medical records.

Statistical Analyses

The OS was the primary end point, defined as the time from diagnosis to death during follow-up or to the date of the last follow-up. Pearson χ^2 test was used for categorical or binary variables and the Mann-Whitney *U*-test was used for continuous variables and intergroup variance analyses. Continuous variables are expressed by median and range, while classified variables are expressed by percentage and frequency (%, n). For practically predicting the prognosis of all variables, receiver operating characteristic (ROC) analysis allowed the selection of the optimal cutoff values. The Kaplan-Meier method was used for survival analysis, and a log-rank test was used for comparing the statistical significance of differences between curves. Univariate and multivariate analyses by stepwise Cox proportional hazards model were conducted for scrutinizing the relative risk of potential hazard factors and the 95% confidence interval (95% CI) of the OS. The correlation between continuous variables was analyzed by Pearson test. The Spearman test was used to analyze the correlation between continuous variables and categorical variables. All displayed *P* values are 2-sided with significance at $P < .05$. Statistical analyses entailed the use of the Software Package IBM SPSS 21.0 (SPSS, USA).

Results

Baseline characteristics

The study cohort included 72 patients with newly diagnosed MM. Clinical parameters and laboratory diagnoses were compared between survivors and nonsurvivors within 2 years (Table 1). Among all patients, men constituted 58% (42) and women 42% (30); the median age at diagnosis was 59 years (range, 37-83 years), the median time from diagnosis to death was 715 days (range, 15-1400 days), and the 2-year overall survival rate was 48.6% (35/72). According to ISS staging, 13 patients (18%), 20 patients (28%), and 39 patients (54%) were

Table1. Comparison of baseline clinical characteristics (2-year survival or death).

VARIABLES	ALL PATIENTS (N=72) MEDIAN (RANGE)	SURVIVORS (N=35) MEDIAN (RANGE)	NON-SURVIVORS (N=37) MEDIAN (RANGE)	*P* VALUE
Age, y	59 (37-83)	58 (37-74)	62 (43-83)	.039
Male	42	21/42 (50%)	21/42 (50%)	NS
Female	30	13/30 (43%)	17/30 (57%)	NS
Survival time within 2y, d	715 (15-1400)	945 (734-1400)	210 (15-730)	<.001
ISS stage				NS
I	13	7	6	
II	20	11	9	
III	39	17	22	
Chemotherapy				NS
BTD	55 (76.3%)	26 (36.1%)	29 (40.2%)	
BD/BCD/RVd/PAD/other	17 (23.6%)	8 (11.1%)	9 (12.5%)	
BPC (%)	35 (5.5-97)	30.5 (5.5-97)	38 (7.5-94.5)	NS
Light chain κ/λ	1.53 (0-558.48)	2.14 (0.01-219.06)	0.865 (0-558.48)	NS
β2MG, mg/L	6.58 (1.14-30.24)	5.49 (1.14-29.25)	28 (12-46)	NS
C4, g/L	0.175 (0.0167-0.45)	0.19 (0.02-0.45)	0.17 (0.167-0.45)	NS
C3, g/L	0.77 (0.0583-2.16)	0.8 (0.26-1.34)	0.72 (0.0583-2.16)	NS
CRP, mg/L	6.22 (0.34-184)	5.89 (0.34-74.9)	7.67 (1.11-184)	NS
Hgb, g/L	83.5 (44-170)	96 (44-170)	77 (49-136)	0.007
PLT, $\times 10^9$/L	150.5 (26-649)	168 (26-293)	134 (37-649)	0.046
ALT, U/L	17.5 (6-309)	16 (6-78)	19 (6-309)	NS
AST, U/L	23 (9-307)	21 (9-66)	27 (11-307)	NS
ALP, U/L	65.0 (19.5-494)	62 (21-134)	79 (19.5-494)	NS
TC, mmol/L	2.9 (0.79-6.99)	2.955 (1.08-5.87)	2.65 (0.79-6.99)	NS
TG, mmol/L	1.19 (0.31-3.41)	1.18 (0.48-2.95)	1.2 (0.31-3.41)	NS
HDL, mmol/L	0.77 (0.36-2.05)	0.785 (0.42-2.05)	0.74 (0.36-1.97)	NS
Albumin, g/L	31.5 (12-46)	33 (15.3-46)	28 (12-46)	NS
Globulin, g/L	60 (18-131)	58 (18-117)	65 (18-131)	NS
BUN, mmol/L	6.4 (2.2-21.9)	5.9 (2.6-18.6)	7.3 (2.2-21.9)	0.046
Cr, μmol/L	89.5 (35-800)	82 (39-401)	120 (35-800)	NS
UA, μmol/L	476(95-814)	477 (95-752)	460 (206-814)	NS
Calcium, mmol/L	2.185 (1.72-3.9)	2.21 (1.72-3.24)	2.55 (1.77-3.9)	NS
APTT, s	36.6 (13.2-65.5)	36.4 (27.3-56.2)	36.6 (13.2-65.5)	NS
PT, s	13.8 (10.9-27.9)	13.5 (10.9-20.6)	14.3 (11.4-27.9)	NS
TT, s	19 (0.8-39.9)	18 (0.8-39.9)	19.9 (14.4-34.6)	NS
FIB, g/L	3.6 (1.14-8.35)	3.53 (1.14-6.86)	3.64 (1.37-8.35)	NS

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BCD, bortezomib/cyclophosphamide/dexamethasone; BD, bortezomib/dexamethasone; BPC, bone marrow plasma cell; BTD, Bortezomib/thalidomide/dexamethasone; BUN, blood Urea Nitrogen; C3, complement 3; C4, complement 4; Cr, Creatinine; CRP, C-reactive protein; FIB, fibrinogen; HDL, high-density lipoprotein; Hgb, hemoglobin; ISS, International staging system; NS, not significant ($P > .05$); PAD, bortezomib/adriamycin/dexamethasone; PLT, platelet; PT, prothrombin time; RVd, lenalidomide/bortezomib/dexamethasone; TC, total cholesterol; TG, triglyceride; TT, thrombin time; UA, uric acid; β2MG, β2-microglobulin.
Continuous variables are expressed by median and range, whereas classified variables are expressed by percentage and frequency (%, n).

Table 2. Univariate analyses displaying factors significantly associated with overall survival (OS) as per the cutoff value of variables between survivors and nonsurvivors.

VARIABLES	ROC CURVE	UNIVARIATE		
	CUTOFF-VALUE	HR	95% CI	*P* VALUE
Age, y	67	0.39	0.20-0.78	.038
BPC, %	30.75	0.38	0.17-0.84	.017
Light chain κ/λ	94.155	0.46	0.21-0.99	.048
C4, g/L	0.095	2.73	1.34-5.54	.006
C3, g/L	0.735	1.98	1.03-3.78	.040
CRP, mg/L	10.5	0.39	0.20-0.76	.005
Hgb, g/L	91.5	2.88	1.36-6.13	.006
PLT, $\times 10^9$/L	115.5	2.44	1.27-4.68	.007
ALT, U/L	27.5	0.45	0.21-0.93	.030
AST, U/L	29.5	0.43	0.23-0.83	.011
ALP, U/L	99	0.47	0.232-0.933	.031
Albumin, g/L	28.1	2.05	1.07-3.92	.030
BUN, mmol/L	9.3	0.44	0.22-0.87	.018
Cr, μmol/L	104.5	0.44	0.23-0.85	.015
PT, s	13.35	0.46	0.22-0.95	.036
TT, s	19.7	0.49	0.25-0.94	.031

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BPC, bone marrow plasma cell; CI, confidence interval; CRP, C-reactive protein; PLT, platelet; PT, prothrombin time; ROC, receiver operating characteristic; TT, thrombin time.

in stages I, II, and III, respectively. Bortezomib/thalidomide/dexamethasone (BTD) was the main chemotherapy regimen in most patients (55/72, 76.3%), and there was no significant difference of BTD on survivors (26/72, 36.1%) and nonsurvivors (29/72, 40.2%). Other chemotherapy regimens include bortezomib/dexamethasone (BD), bortezomib/cyclophosphamide/dexamethasone (BCD), lenalidomide/bortezomib/dexamethasone (RVd), bortezomib/adriamycin/dexamethasone (PAD), and so on, and there was no significant difference of BD/ BCD/RVd/PAD on survivors (8/72, 11.1%) and nonsurvivors (9/72,12.5%). Comparison of factors unveiled conspicuous intergroup variances. The nonsurvivors were older (median age in years: 62 vs 58; survivors and nonsurvivors, respectively, $P = .039$) and showed elevated BUN (7.3 mmol/L vs 5.9 mmol/L; $P = .046$), but lowered Hgb (77 g/L vs 96 g/L; $P = 0.007$) and PLT (134 $\times$ 10^9/L vs168 $\times$ 10^9/L; $P = .046$). The remaining factors displayed no such evident variations.

Univariate analysis for risk factors. To explore whether there are risk factors between survivors and nonsurvivors, we assessed the impact of each indicator on survival. Table 2 and Supplementary Table 1 display the results of univariate analysis of the potential predictors of death in patients with MM. These are age ($P = .038$), BPC ($P = .017$), light chain κ/λ ($P = .048$), complement 4 ($P = .006$), complement 3 ($P = .040$), CRP ($P = .005$), Hgb ($P = .006$), PLT ($P = .007$), ALT ($P = 0.030$), AST ($P = .011$), ALP ($P = .031$), albumin ($P = .030$), BUN ($P = .018$), creatinine ($P = .015$), PT ($P = .036$), and TT ($P = 0.031$) that displayed a significant correlation with OS. Furthermore, the survival curves of different risk factors for survivable and nonsurvivable patients with MM as depicted in Figure 1A to D and Supplementary Figure 1A to L as per the Kaplan-Meier method display consistency with the significant risk factors as per the univariate analysis obtained.

To elucidate, age ⩾67 years ($P = .006$), BPC ⩾30.75% ($P = .012$), light chain κ/λ ⩾94.155 ($P = .041$), complement 4 ⩽0.095 g/L ($P = .004$), complement 3 ⩽0.735 g/L ($P = .035$), CRP ⩾10.5 mg/L ($P = .004$), Hgb ⩽91.5 g/L ($P = .004$), platelet ⩽115.5 $\times$ 10^9/L ($P = .005$), ALT ⩾27.5 U/L ($P = .025$), AST ⩾29.5 U/L ($P = .009$), ALP ⩾99 U/L ($P = .026$), albumin ⩽28.1 g/L ($P = .026$), BUN ⩾9.3 mmol/L ($P = .014$), creatinine ⩾104.5 μmol/L ($P = .012$), PT ⩾13.35 s ($P = .031$), and TT ⩾13.35 s ($P = .026$) have lower cumulative survival probability, respectively.

Multivariate survival analysis. The aforementioned factors were subjected to regression as described in the "Materials and Methods" section to scrutinize independent predictors

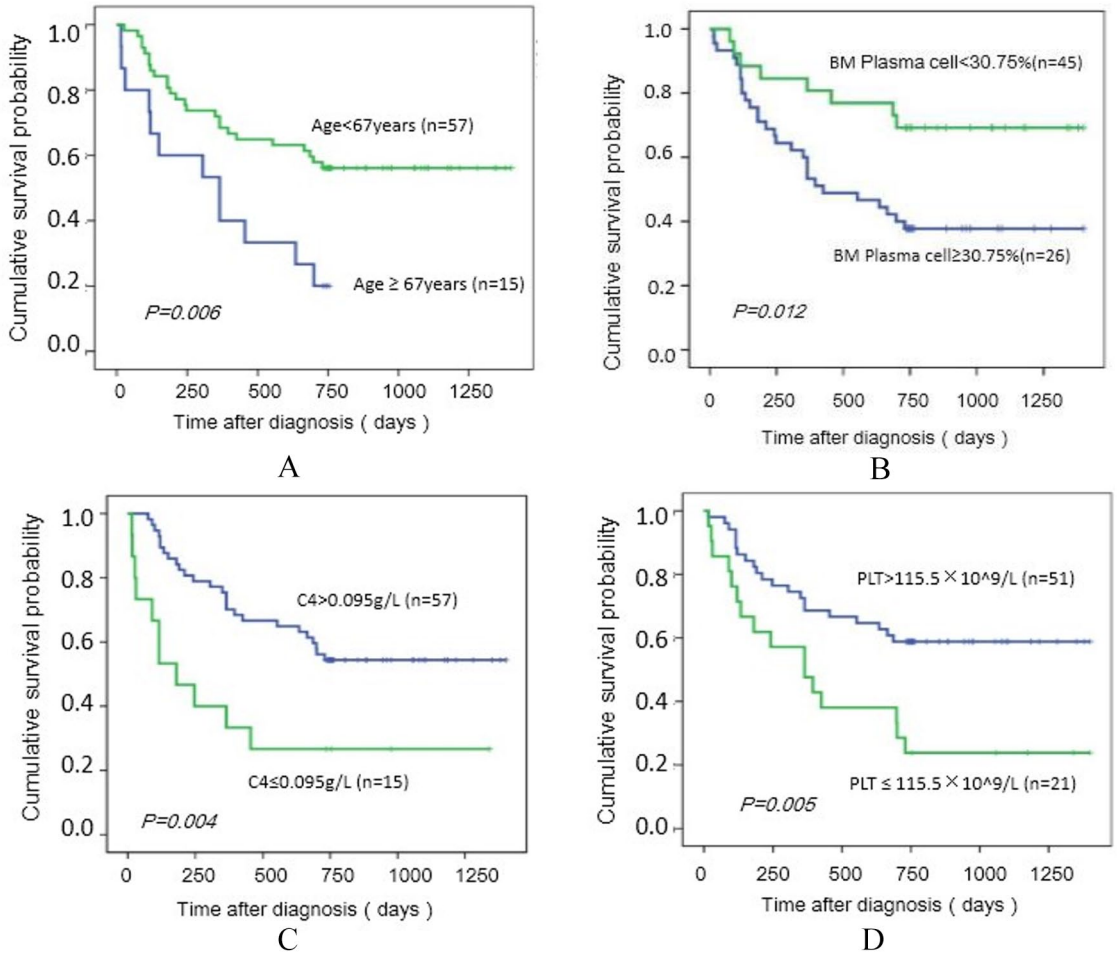

Figure 1. Kaplan-Meier survival curves of patients with MM with significant factors evidenced by multivariate analysis. Overall survival (OS) in patients with (A) age ⩾67 years or age <67 years, (B) bone marrow plasma cell percentage ⩾30.75% or bone marrow plasma cell percentage <30.75%, (C) complement C4 ⩽0.095 g/L or complement C4 >0.095 g/L, and (D) platelet ⩽115.5×10⁹/L or platelet >115.5×10⁹/L.

of mortality in patients with MM. These were inclusive of platelet ⩽115.5 × 10⁹/L (hazard ratio [HR] = 5.82, 95% CI = 2.522-13.436, $P < .001$), complement 4 ⩽0.095 g/L (HR = 3.642, 95% CI = 1.486-8.924, $P = .005$), age ⩾67 years (HR = 0.191, 95% CI = 0.078-0.47, $P < .001$), and BPC ⩾30.75% (HR = 0.171, 95% CI = 0.06-0.482, $P = .001$) (Table 3).

Comparison of clinical parameters in patients with different levels of C4. By comparing the clinical parameters of patients with high and low levels of C4, the results showed that ISS stage, levels of C3, albumin, globulin, and calcium of patients with different C4 levels were significantly different. International Staging System stage, levels of C3, and globulin in patients with C4 ⩽0.095 g/L were higher than those in patients with C4 >0.095 g/L ($P < .05$). Levels of albumin and calcium in patients with C4 ⩽0.095 g/L were significantly lower than those with C4 >0.095 g/L (Table 4, $P < .05$).

Correlation analysis between levels of C4 and clinical parameters. We further analyzed the correlation between levels of C4 and ISS stage, levels of C3, albumin, globulin, and calcium, respectively.

Table 3. Multivariate analysis for overall survival (OS) using the Cox proportional hazards model.

	HR	95% CI	*P* VALUE
Age ⩾67 y	0.191	0.078-0.47	<.001
BPC ⩾30.75%	0.171	0.06-0.482	.001
C4 ⩽0.095 g/L	3.642	1.486-8.924	.005
PLT ⩽115.5 × 10⁹/L	5.821	2.522-13.436	<.001

Abbreviations: BPC, bone marrow plasma cell; CI, confidence interval; PLT, platelet; HR, hazard ratio.
Through multivariate analysis of risk factors, a significantly different level of platelet and complement C4 was observed in survivors and nonsurvivors with a hazard ratio of 5.821 and 3.642, respectively. Age and proportion of bone marrow plasma cell are also significantly different among survivors and nonsurvivors, with hazard ratios of 0.191 and 0.171, respectively.

The results showed that serum levels of C4 were significantly negatively correlated with ISS stage ($rs = -0.320$) and levels of globulin ($r = -0.653$) ($P < .05$). The levels of C4 were significantly positively correlated with levels of C3 ($r = 0.530$) and albumin ($r = 0.446$) ($P < .05$), and were not obviously correlated with levels of calcium (Table 5).

Table 4. Comparison of clinical data between patients with different C4 levels.

VARIABLES	C4 >0.095 G/L (N=57)	C4 ≤0.095 G/L (N=15)	*P* VALUE
Age, y	58 (52-64)	63 (54-69)	NS
Survival time within 2 y, d	743 (357-968)	180 (30-735)	.004
ISS stage			.015
I	13	0	
II-III	44	15	
BPC, %	35 (19.5-54)	36.8 (22.6-55.6)	NS
β2MG, mg/L	7.8 (3.1-13.1)	6.39 (3.9-8.2)	NS
C3, g/L	0.8 (0.6-1.0)	0.64 (0.36-0.77)	.024
CRP, mg/L	6.35 (2.11-11.7)	5.8 (1.9-14.5)	NS
Hgb, g/L	87 (72-107)	82 (70-101)	NS
PLT, $\times 10^9$/L	151 (111-199)	139 (109-195)	NS
Albumin, g/L	33 (25-39)	26 (24-29)	.008
Globulin, g/L	43 (30-69)	85 (75-102)	<.001
BUN, mmol/L	6.6 (5.0-10.8)	6.1 (4.8-7.7)	NS
Cr, μmol/L	91 (74-189)	82 (58-130)	NS
UA, μmol/L	486(367-650)	440 (338-648)	NS
Calcium, mmol/L	2.24 (2.06-2.45)	1.98 (1.87-2.11)	<.001

Abbreviations: BPC, bone marrow plasma cell; CRP, C-reactive protein; ISS, International Staging System; NS, not significant; PLT, platelet.

Table 5. The relationship between C4 level and clinical parameters in the patients.

PARAMETERS	CORRELATION COEFFICIENT	*P* VALUE
ISS	−0.320	.006
C3	0.530	<.001
Albumin	0.446	<.001
Globulin	−0.653	<.001
Calcium	0.202	.088

Abbreviation: ISS, International staging system.

Discussion

Our study revealed the involvement of advanced age, low PLT level, and a high proportion of BPCs in poor prognosis in patients with MM in lieu of other studies.[5,6,8] Besides, low complement 4 levels were found to emerge as a risk for poor MM outcome as evidenced by the multivariate model. In addition, levels of C4 were negatively correlated with ISS stage (r_s = −0.320) and levels of globulin (r = −0.653) (P < .05), and positively correlated with levels of C3 (r = 0.530) and albumin (r = 0.446).

As a part of innate and adaptive immune functioning, the vital involvement of the complement system to control inflammation by participating in humoral immunity and maintaining the in vivo immune balance is known. The activation of the complement system is a highly conserved mechanism, predominantly entailing the classical pathway, lectin, and terminal pathways of which the first displays the maximum range and efficacy. This entails the recruitment of C1qC1r2C1s2 (C1 complex) by the antibody-pathogen complex to start off a cleavage cascade inclusive of C2, C3, C4, and C5 to set off microbial clearance.[17] As one of the core components of the complement cascade, complement C4 is involved in the activation of classical and lectin pathways, which is an important cofactor in nonspecific and humoral immunity and is essential for fighting against infection. Overactivation or deficiency of complement may lead to many pathologies, including abnormal inflammation, tumor progression, tissue damage, and infection.[18] Complement components are mainly produced by the liver, but it is worth noting that some tumor cells and stromal cells also have the ability to produce complement proteins. Therefore, in different tumor types, complement may be anti-tumor or pro-tumor; despite the sameness of the tumor type, a slew of complement effects can be expected.[19]

Patients with MM often manifest an infection, which is mainly caused by hypogammaglobulinemia attributed to plasma cell clone proliferation and various aberrant immune functions.[20] It has been found that there are abnormalities in complement composition and function,[13] and complement level[14] in patients with MM, leading to an in vivo imbalance of the immune system. Myeloma progression can involve an aspect of steering by the complement level. Yang et al[21] revealed the plausible prediction of progression by low levels of C1q. The current work revealed an evidently lower cumulative survival probability of patients with MM with low levels of C4 as opposed to those with elevated C4 expression with the 2-year mortality risk augmented in patients with MM by a factor 3.642 times against other patients.

Our correlation analysis results showed that levels of C4 were significantly correlated with ISS stage, levels of globulin, C3, albumin, and globulin, especially levels of globulin. The abnormality of these indicators suggests that the patients may be in infection and have a severe inflammatory response. As a result, a deficiency of C4 in patients with MM may result in an immunocompromised state and a high risk of severe infection. B-cell memory response is weak after C4 deficiency, which may be due to impaired memory B-cell response stimulation and lead to aggravating infection.[22] C4 produced by macrophages of the bone marrow can restore humoral responses to infection, suggestive of the necessity of local complement C4 production to activate an effective B-cell response.[23] In addition, C4 is also required for the activation, proliferation, and survival of normal T cells.[24] Recent works have displayed the direct suppression of human adenovirus infection by C4 via inactivation of the viral capsid independently of all downstream

complement components.[25] Moreover, low levels of C4 in patients with myeloma are associated with neutrophil adhesion defects,[26,27]and the ability of macrophages to absorb apoptotic cells was reduced in C4-deficient individuals,[28] which may lead to recurrent refractory infections in patients.[27] This led us to propose the involvement of elevated infection causing the poor prognosis in MM on account of the reduced C4 levels.

The first limitation of this work was its retrospective nature with small sample size. Second, due to the lack of cytogenetic data in most patients, it was not possible to analyze the impact of adverse cytogenetic abnormalities and revised ISS on prognosis. Finally, more trials and large-scale clinical trials of complement C4 activation are required in the future. This warrants prospective clinical trials encompassing a slew of factors to corroborate the lowered C4 level in early MM and its prognostic value. This can hence facilitate tailor-made myeloma treatment with efficacy.

Conclusion

This retrospective study displayed the potential of complement C4 to emerge as an independent predictor of OS in patients with MM. This can herald possible poor prognosis in newly diagnosed patients with MM. The easy detection of serum complement C4 and its ubiquitous clinical usage can facilitate future therapy in these patients manifesting low C4 to reduce their mortality. Another avenue here is the potential of immunotherapy for MM. The exact prognostic functioning of C4 in MM necessitates future analyses.

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Author contributions

L.Z. performed the research and wrote the article. L.Z., X.L., and F.L. contributed clinical data. T.Y., K.S., S.Z., and L.Y. cared for the patients and critically reviewed the manuscript. H.H. and Z.L. designed the research study. H.H., Z.L., and L.Z. contributed to the analysis and data interpretation. All authors contributed to the review, provided their comments on this, and approved the final version.

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Supplemental material

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