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

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Abstract

Background and aim: 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 MM patients, but the precise association necessitates elucidation. Therefore, this study scrutinizes the correlation between serum complement level and the disease outcome of MM patients.

Materials and methods: A retrospective analysis of 72 MM patients (new diagnosis) with complement C4 and C3 along with common laboratory indicators was done. The Pearson's $\chi 2$ test and the Mann–Whitney U test were done to evaluate categorical or binary variables and inter-group variance, respectively. Kaplan-Meier test and Cox's proportional hazards regression were employed for quantitation of overall survival (OS) and univariate or multivariate analyses, respectively.

Results: The Cox proportional hazard model analysis unveiled the following: platelet≤115.5×10^9/L(HR=5.82，95%CI=2.522-13.436, P<0.001)， complement C4≤0.095g/L(HR=3.642, 95%CI=1.486-8.924,P=0.005), age≥67 years(HR=0.191, 95%CI=0.078-0.47, P<0.001)，bone marrow plasma cell percentage≥30.75% (HR=0.171, 95%CI=0.06-0.482, P=0.001) can be employed 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 MM patients. Interestingly, a low complement 4 level can function as a new indicator of poor prognosis in MM patients.

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

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 to judge the prognosis for modifying the therapy. Nowadays, the primary methods used to stage MM patients 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, low hemoglobin, high bone marrow plasma cells 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 MM patients [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.

found that chronic lymphocytic leukemia patients 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[10]. Moreover, studies have shown that variation in complement genes (such as MASP2, C5, and C9) is closely related to the development of NHL [11]. Variations in C9 and complement regulatory genes, e.g., Event-free survival (EFS) in FL display an association with CFHR5, Factor H, CD55, CD46, and CFHR1 while EFS for DLBCL is linked to C7 variants [12].

Research has revealed that the aberrant profile of the complement system, as an integral part of the immune response in MM patients. Zurlo et al. demonstrated aberrant serum complement deposition and composition in myeloma patients, which was negatively correlated with monoclonal protein concentration, with no evident correlation with disease activity or infection[13]. Lugassy et al. scrutinized the complement system of 22 myeloma patients 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 myeloma patients [14]. In addition, the defective binding effect of complement and *Streptococcus pneumoniae* in MM patients 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 MM patients, 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 MM patients.

Methods

Patients

We retrospectively analyzed 72 MM patients (newly diagnosed in accordance with the International Myeloma Working Group criteria [16]) at the Department of Hematology at the First People's Hospital of Yunnan Province between July 1st, 2017 and January 1st, 2019. 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 done. Scoured clinical parameters included age, sex, percentage of bone marrow plasma cells(BPC), ISS stage, light chain κ/λ, β2-microglobulin, complement C4, complement C3, C-reactive protein (CRP), hemoglobin (Hgb), platelet (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. This study received permissions from the Ethics Committee of the First People's Hospital of Yunnan Province 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 overall survival (OS) was the primary endpoint, defined as the time from diagnosis to death during follow-up, or to the date of the last follow-up. Pearson's $\chi 2$ test was used for categorical or binary variables and the Mann–Whitney U test was used for continuous variables and inter-group 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. Kaplan-Meier method was employed for survival analysis, and a Log-rank test was employed for comparing the statistical significance of differences between curves. Univariate and multivariate analyses by stepwise Cox's proportional hazards model were conducted for scrutinizing the relative risk of potential hazard factors and 95% CI (the 95% confidence interval) of the OS. proportional hazards. All displayed P-values are two-sided with significance at $P < 0.05$. Statistical analyses entailed the use of the Software Package IBM SPSS 21.0 (SPSS, U.S.A).

Results

Baseline characteristics

The study cohort included 72 patients with newly diagnosed MM. Clinical parameters and laboratory diagnoses were compared between survivors and non-survivors within two years (Table 1). Among all patients, males constituted 58 % (42) and 42% females (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 in stages I, II, and III, respectively. Comparison of factors unveiled conspicuous inter-group variances. The non-survivors were older (median age in years: 62 vs. 58; survivors and non-survivors, respectively, $P = 0.039$) and showed elevated blood urea nitrogen (7.3 mmol/L vs.5.9 mmol/L; $P = 0.046$); but lowered hemoglobin (77 g/L vs. 96 g/L; $p = 0.007$)and platelets(134×10^9/L vs.168×10^9/L; $p = 0.046$). The remaining factors displayed no such evident variations.

Table 1
Comparison of baseline clinical characteristics (Two-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 (years)	59 (37–83)	58(37–74)	62(43–83)	0.039
Male	42	21/42(50%)	21/42(50%)	NS
Female	30	13/30(43%)	17/30(57%)	NS
survival time within 2 years,Days	715(15-1400)	945(734–1400)	210(15–730)	< 0.001
ISS stage	13	7	6	NS
I	20	11	9	
II	39	17	22	
III				
BPC (%)	35(5.5–97)	30.5(5.5–97)	38(7.5–94.5)	NS
Light chainκ/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 (×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

Variables	All patients (N = 72) median (range)	Survivors (N = 35) median (range)	Non-survivors (N = 37) median (range)	*P-value*
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 (umol/L)	89.5(35–800)	82(39–401)	120(35–800)	NS
UA(umol/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

Table 1. Continuous variables are expressed by median and range, while classified variables are expressed by percentage and frequency (%, n).

Abbreviations:

ISS, International staging system; BPC,bone marrow plasma cell;β2MG, β2-microglobulin; C4, complement 4; C3, complement 3; CRP, C-reactive protein; Hgb, hemoglobin; PLT ,platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, Alkaline phosphatase; TC,Total cholesterol; TG,Triglyceride; HDL, high density lipoprotein; BUN,Blood Urea Nitrogen; Cr,Creatinine; UA, Uric Acid; APTT,activated partial thromboplastin time; PT,prothrombin time; TT, thrombin time ;FIB,fibrinogen.

NS: not significant;($P > 0.05$).

Univariate analysis for risk factors

To explore whether there are risk factors between survivors and non-survivors, 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 MM patients. These are age (P = 0.038), BPC (P = 0.017), Light chain κ/λ (P = 0.048), complement 4 (P = 0.006), complement 3 (P = 0.040), CRP (P = 0.005), Hgb (P = 0.006), PLT (P = 0.007), ALT (P = 0.030), AST (P = 0.011), ALP (P = 0.031), albumin (P = 0.030), blood urea nitrogen (P = 0.018), creatinine (P = 0.015), prothrombin time (P = 0.036), and thrombin time (P = 0.031)

that displayed a significant correlation with OS. Further, the survival curves of different risk factors for survivable and non-survivable MM patients as depicted in Figs. 1A- D and Supplementary Figs. 1A-L as per the Kaplan-Meier method display consistency with the significant risk factors as per the univariate analysis obtained.

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

	ROC Curve	**Univariate**		
Variables	Cutoff-value	HR	95% CI	P-value
Age (years)	67	0.39	0.20–0.78	0.038
BPC (%)	30.75	0.38	0.17–0.84	0.017
Light chainκ/λ	94.155	0.46	0.21–0.99	0.048
C4 (g/L)	0.095	2.73	1.34–5.54	0.006
C3 (g/L)	0.735	1.98	1.03–3.78	0.040
CRP(mg/L)	10.5	0.39	0.20–0.76	0.005
Hgb (g/L)	91.5	2.88	1.36–6.13	0.006
PLT (×10^9/L)	115.5	2.44	1.27–4.68	0.007
ALT (U/L)	27.5	0.45	0.21–0.93	0.030
AST (U/L)	29.5	0.43	0.23–0.83	0.011
ALP (U/L)	99	0.47	0.232–0.933	0.031
Albumin(g/L)	28.1	2.05	1.07–3.92	0.030
BUN(mmol/L)	9.3	0.44	0.22–0.87	0.018
Cr (umol/L)	104.5	0.44	0.23–0.85	0.015
PT(S)	13.35	0.46	0.22–0.95	0.036
TT(S)	19.7	0.49	0.25–0.94	0.031

Table 2. The Cutoff-value of cytokines was determined by the ROC curve, and survival analysis was performed by the Kaplan-Meier method.

To elucidate, age ≥ 67years (P = 0.006), BPC ≥ 30.75% (P = 0.012), Light chain κ/λ ≥ 94.155 (P = 0.041), complement 4 ≤ 0.095 g/L (P = 0.004), complement 3 ≤ 0.735 g/L(P = 0.035), CRP ≥ 10.5 mg/L (P = 0.004), hemoglobin ≤ 91.5 g/L (P = 0.004), platelet ≤ 115.5×10^9/L (P = 0.005, alanine aminotransferase ≥ 27.5 U/L (P = 0.025), aspartate aminotransferase ≥ 29.5 U/L (P = 0.009), alkaline phosphatase ≥ 99

U/L (P = 0.026), albumin ≤ 28.1 g/L (P = 0.026), blood urea nitrogen ≥ 9.3 mmol/L (P = 0.014), creatinine ≥ 104.5 umol/L (P = 0.012), prothrombin time ≥ 13.35 s (P = 0.031), thrombin time ≥ 13.35 s (P = 0.026) have lower cumulative survival probability, respectively.

Multivariate survival analysis

The aforementioned factors were subjected to regression as described in the materials section to scrutinize independent predictors of mortality in MM patients. These were inclusive of platelet ≤ 115.5×10^9/L(HR = 5.82,95% CI = 2.522–13.436, P < 0.001)， complement 4 ≤ 0.095g/L(HR = 3.642, 95%CI = 1.486–8.924, P = 0.005), age ≥ 67 years (HR = 0.191, 95%CI = 0.078–0.47, P < 0.001,BPC ≥ 30.75% (HR = 0.171, 95%CI = 0.06–0.482, P = 0.001)(Table 3).

Table 3
Multivariate analysis for overall survival (OS) using the Cox Proportional Hazards Model.

	HR	95% CI	P-value
Age ≥ 67 years	0.191	0.078–0.47	< 0.001
BPC ≥ 30.75%	0.171	0.06–0.482	0.001
C4 ≤ 0.095g/L	3.642	1.486–8.924	0.005
PLT ≤ 115.5×10^9/L	5.821	2.522–13.436	< 0.001

Table 3. Through multivariate analysis of risk factors, significantly different level of platelet and complement C4 was observed in survivors and non-survivors 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 non-survivors, with hazard ratios of 0.191 and 0.171,respectively.

Discussion

Our study revealed the involvement of advanced age, low platelet level, and a high proportion of bone marrow plasma cells in poor prognosis in MM patients 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.

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. Over-activation 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].

MM patients 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 MM patients, 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. revealed the plausible prediction of progression by low levels of C1q[21]. The current work revealed an evidently lower cumulative survival probability of MM patients with low levels of C4 as opposed to those with elevated C4 expression with the two-year mortality risk augmented in MM patients by a factor 3.642 times against other patients.

A deficiency of C4 in MM patients 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 myeloma patients are associated with neutrophil adhesion defects [26, 27], which may lead to recurrent refractory infections in myeloma patients [28]. 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. Lastly, 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 MM patients. This can herald possible poor prognosis in newly diagnosed MM patients. The easy detection of serum complement C4 and its ubiquitous clinical usage can facilitate future therapy in

these patients manifesting low C4 in order 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.

Declarations

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Declaration of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

LZ performed the research and wrote the paper.LZ,XL, FLcontributed clinical data. TY,KS,SZ and LY cared for the patients and critically reviewed the manuscript.HH and ZL designed the research study. HH, ZL and LZ contributed to the analysis and data interpretation. All authors contributed to the review, provided their comments on this manuscript and approved the final version.

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Supplementary Table

The supplementary table is not available with this version.

Figures

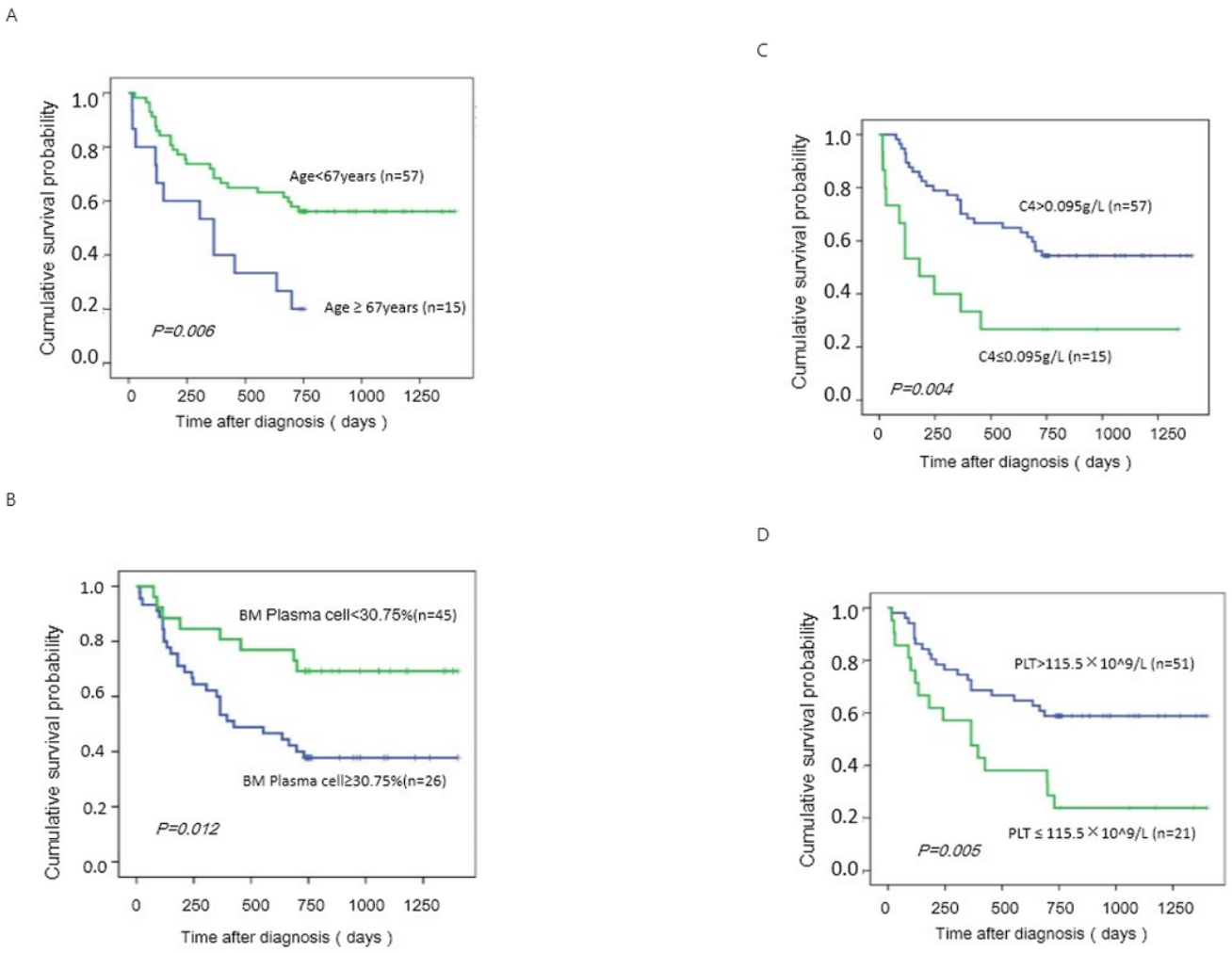

Figure 1

Kaplan-Meier survival curves of MM patients with significant factors evidenced by multivariate analysis. Kaplan-Meier curve of patients 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≤0.095g/L or complement C4>0.095g/L, (D) platelet≤115.5×10^9/L or platelet>115.5×10^9/L.

Supplementary Files

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- SupplementaryFigure1.docx