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Initial Circulating CD138 Predicts End-Stage Kidney Disease in Patients with Microscopic Polyangiitis

Jung Yoon Pyo[1], Yong-Beom Park[2,3], and Sang-Won Lee[2,3]

[1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam;
[2]Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul;
[3]Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Korea.

Purpose: CD138 is a cell surface proteoglycan involved in plasma cell survival and cell adhesion, and can be detected in serum via ectodomain shedding. This study aimed to investigate the clinical utility of circulating CD138 at diagnosis in predicting future progression to end-stage kidney disease (ESKD) in patients with microscopic polyangiitis (MPA).

Materials and Methods: Sixty-five patients newly diagnosed with MPA were included. Antineutrophil cytoplasmic antibody-associated vasculitis-specific indices and clinical and laboratory data were collected. Circulating CD138 levels were measured from stored sera at the time of diagnosis and a cut-off value for predicting ESKD progression was determined using receiver operating characteristic curve analysis.

Results: The median circulating CD138 level at diagnosis was 62.8 ng/mL. Circulating CD138 at diagnosis showed positive correlations with the cross-sectional Birmingham Vasculitis Activity Score, Five-Factor Score, erythrocyte sedimentation rate, C-reactive protein level, and baseline serum creatinine level, while demonstrating a negative correlation with serum albumin level. Overall, 12 (18.5%) of 65 patients progressed to ESKD. The incidence of progression to ESKD was higher in patients with circulating CD138 ≥73.3 ng/mL at diagnosis than in those without (relative risk=10.588). Additionally, patients with circulating CD138 ≥73.3 ng/mL at diagnosis exhibited significantly lower ESKD-free survival rates than those without (p=0.002).

Conclusion: This study demonstrated that circulating CD138 measured at diagnosis has clinical utility as a biomarker for predicting future progression to ESKD in patients with MPA, and incorporating CD138 measurement at diagnosis may assist in identifying high-risk patients and guiding early therapeutic interventions in clinical practice.

Key Words: CD138, antineutrophil cytoplasmic antibody, vasculitis, activity, dialysis

INTRODUCTION

CD138, which is used identically to syndecans-1, is a representative canonical plasma cell surface marker that plays an important role in the survival of plasma cells and a complementary role in cell-cell adhesion. Among haematopoietic cells, CD138 is expressed at high levels in plasma cells and at low levels in pre-B cells. Circulating CD138 plays a role in systemic lupus erythematosus (SLE), a representative autoreactive antibody-mediated autoimmune disease.[1] A previous study has revealed the clinical utility of circulating CD138. This study demonstrated that circulating CD138 levels were higher in patients with active SLE than in healthy controls.[2] Another study revealed that circulating CD138 is associated with lupus nephritis.[3] Another study suggested a more specific mechanism.[1] This study demonstrated that circulating CD138 may be secreted into the bloodstream by cleaving enzymes such as trypsin from immune cells expressing CD138 on their surface, and subsequently, that the secreted circulating CD138 may help to augment the interaction between a proliferation-inducing ligand (APRIL) and transmembrane activator, calcium modulator, cyclophilin ligand interactor (TACI), promoting autore-

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Corresponding author: Sang-Won Lee, MD, PhD, Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun–gu, Seoul 03722, Korea.
E-mail: sangwonlee@yuhs.ac

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active antibody production and contributing to the progression of SLE.[1,4] In summary, these results suggest that circulating CD138 has clinical utility as a surrogate marker for activation, aggravation, and progression of autoreactive antibody-mediated autoimmune diseases with renal involvement.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small-vessel vasculitis that is histologically characterised by fibrinoid necrosis with few or no immune complex deposits and primarily affects capillaries, arterioles, venules, and occasionally medium-sized arteries.[5,6] AAV has three subtypes according to clinical, laboratory, radiological, and histological features: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[7-9] Among these, MPA primarily affects the lungs and kidneys. AAV may also be categorised into three groups according to the ANCA type: myeloperoxidase (MPO)-ANCA vasculitis, proteinase 3 (PR3)-ANCA vasculitis, and ANCA-negative vasculitis.[10]

We previously demonstrated the clinical usefulness of initial circulating CD138 levels in reflecting cross-sectional AAV activity and predicting all-cause mortality during follow-up in patients with AAV. However, we were unable to establish the predictive value of circulating CD138 for progression to dialysis-requiring renal impairment. Interestingly, when focusing only on 38 patients with MPA, we found the clinical potential of circulating CD138 at diagnosis as a biomarker for predicting future progression to end-stage kidney disease (ESKD): in receiver operating characteristic (ROC) curve analysis, the area under the curve (AUC) was 0.724 (p=0.068) and initial circulating CD138 was correlated with the sum of scores assigned to an item of renal manifestation of the nine items of the Birmingham Vasculitis Activity Score (BVAS).[11,12] Therefore, we included more patients with MPA in this study and attempted to demonstrate the clinical utility of circulating CD138 at diagnosis as a biomarker for predicting future progression to ESKD.

MATERIALS AND METHODS

Patients

This study included 65 patients with MPA from a single-centre cohort of Korean patients with AAV. The inclusion criteria were as follows: 1) patients first diagnosed with MPA at the Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Severance Hospital by rheumatology specialists from November 2005 to December 2023; 2) fulfilling the classification algorithm for AAV proposed by the European Medicine Agency,[6] the revised nomenclature of systemic vasculitides suggested by the Chapel Hill Consensus Conference,[5] and the 2022 American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR);[7] 3) patients in whom the medical forms for AAV-specific indices were completed and the tests for ANCA were performed within 1 week after or before MPA diagnosis; and 4) those who had the electronic medical charts sufficient for collecting clinical data at MPA diagnosis and during follow-up, including the date of initiation of renal replacement therapy for dialysis patients. The exclusion criteria were as follows: 1) patients with severe medical conditions—such as malignancies, serious infectious diseases, or overlap syndromes of other systemic vasculitides—at the time of MPA diagnosis; 2) patients who had received immunosuppressive drugs for treatment within 4 weeks before MPA diagnosis; and 3) patients with ESKD which occurred before MPA diagnosis.

This study was approved by the Institutional Review Board (IRB) of Severance Hospital, Seoul, Republic of Korea (IRB number 4-2016-0901), and all methods were performed in accordance with the Declaration of Helsinki. All patients in this study provided written informed consent upon enrolment in the AAV cohort at the time of diagnosis and blood sampling. The need for additional written informed consent for this study was waived by the IRB if it had already been obtained at enrolment.

Clinical data at MPA diagnosis

Age and sex were collected as demographic data at diagnosis. The titres and positivity of ANCAs and AAV-specific indices, including the BVAS and the Five-Factor Score (FFS),[13] were recorded. Comorbidities, defined as those recognised before or at MPA diagnosis, including type 2 diabetes mellitus, hypertension, and dyslipidaemia, were also recorded. The results of laboratory tests, including complete blood counts, serum creatinine, serum protein, serum albumin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels, were recorded.

ANCA measurement

MPO-ANCA and PR3-ANCA were measured by a highly sensitive, anchor-coated Phadia ELiA immunoassay (Thermo Fisher Scientific/Phadia, Freiburg, Germany) on a Phadia250 analyser. Perinuclear (P)-ANCA and cytoplasmic (C)-ANCA were detected using indirect immunofluorescence assays. Based on the ACR/EULAR classification criteria, the results obtained using both assay methods were officially recognised.

Circulating CD138 measurement

According to the protocol of the AAV cohort of this hospital, when written informed consent was provided for AAV diagnosis, whole blood was collected from the patients with permission. On the same day, sera were immediately isolated from whole blood and stored at -80°C. Serum levels of circulating CD138 were measured using an enzyme-linked immunosorbent assay kit (Diaclone, Besançon, France).

Clinical data during follow-up

In this study, only future progression to ESKD was evaluated as

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one of the several poor outcomes of MPA. ESKD was defined as a medical condition requiring renal replacement therapy.[14] The follow-up duration based on ESKD was defined as the period from MPA diagnosis to the initiation of renal replacement therapy in patients with ESKD and to the last visit in those without ESKD. Administration of glucocorticoids and immunosuppressive drugs was also investigated.

Statistical analyses

Most statistical analyses were performed using SPSS version 26 (IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corporation, Redmond, WA, USA). Additional survival-based analyses, including the Contal and O'Quigley method for cut-off optimization and time-dependent performance metrics such as time-dependent AUC and integrated AUC, were conducted using R software (version 4.4, Vienna, Austria). Continuous and categorical variables are expressed as medians (Q1–Q3) and numbers (percentages). The correlation coefficients (r) between two variables were determined using Pearson's correlation analysis. The AUC was calculated by ROC analysis. The cut-off was determined by ROC curve analysis as the value maximising the sum of sensitivity and specificity; the relative risk (RR) associated with this cut-off for progression to ESKD was analysed using contingency tables and the chi-square test. As a supplementary approach, the optimal cut-off for circulating CD138 was also explored using the method proposed by Contal and O'Quigley, which identifies the threshold that maximizes the log-rank statistic. Although this method yielded a cut-off of 72 ng/mL, the originally determined ROC-based threshold of 73.3 ng/mL demonstrated superior discriminatory performance and was therefore retained for all subsequent analyses. A comparison of the cumulative survival rates between the two groups was performed using Kaplan–Meier survival analysis with the log-rank test. Cox proportional hazards model analysis was performed to determine the hazard ratio (HR). To further ensure the validity of the multivariable analysis, we examined multicollinearity using variance inflation factors (VIF). All variables included in the final Cox regression model—BVAS, FFS, serum creatinine, serum albumin, and CD138 cut-off (binary)—showed VIF values well below the conventional threshold of concern (all VIFs <4), indicating that multicollinearity was not present. Statistical significance was set at p-value<0.05.

RESULTS

Characteristics

Regarding the variables at diagnosis, the median age of the 65 patients with MPA was 71.0 years, and 26 and 39 patients were males and females, respectively. The median MPO-ANCA and PR3-ANCA titres were 7.0 and 0.0, respectively, and MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA) were positive

Table 1. Characteristics of Patients with MPA at Diagnosis and during Follow-Up (n=65)

Variables	Values
At the time of diagnosis	
Demographic data	
Age (yr)	71.0 (63.0–75.0)
Male sex	26 (40.0)
Female sex	39 (60.0)
ANCA titre and positivity	
MPO-ANCA titre	7.0 (0–94.0)
PR3-ANCA titre	0.0 (0.0–0.0)
MPO-ANCA (or P-ANCA) positive	56 (86.2)
PR3-ANCA (or C-ANCA) positive	2 (3.1)
Both ANCAs	2 (3.1)
No ANCA	9 (13.8)
AAV-specific indices	
BVAS	5.0 (2.0–17.0)
FFS	1.0 (0.0–2.0)
Comorbidities	
Type 2 diabetes mellitus	18 (27.7)
Hypertension	32 (49.2)
Dyslipidaemia	12 (18.5)
Acute-phase reactants	
ESR (mm/hr)	31.0 (14.0–82.0)
CRP (mg/L)	7.8 (1.6–53.0)
Laboratory results	
White blood cell count (/mm^3)	8290.0 (5960.0–11870.0)
Haemoglobin (g/dL)	10.9 (9.1–13.2)
Platelet count (×1000/mm^3)	239.0 (186.0–352.0)
Blood urea nitrogen (mg/dL)	28.0 (18.1–35.9)
Serum creatinine (mg/dL)	1.3 (0.8–2.5)
Total serum protein (g/dL)	6.8 (6.2–7.4)
Serum albumin (g/dL)	3.9 (3.1–4.3)
Circulating CD138 (ng/mL)	62.8 (41.7–120.1)
During follow-up	
ESKD	12 (18.5)
Follow-up duration based on ESKD (months)	24.3 (5.5–47.7)
Medications	
Glucocorticoids	63 (96.9)
Cyclophosphamide	43 (66.2)
Rituximab	9 (13.8)
Mycophenolate mofetil	16 (24.6)
Azathioprine	38 (58.5)
Tacrolimus	6 (9.2)
Methotrexate	3 (4.6)

MPA, microscopic polyangiitis; ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; PR3, proteinase 3; P, perinuclear; C, cytoplasmic; AAV, ANCA-associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ESKD, end-stage kidney disease.
Values are expressed as median (25th–75th percentile) or n (%).

in 56 (86.2%) and 2 (3.1%) patients, respectively. The median BVAS, FFS, ESR, and CRP levels were 5.0, 1.0, 31.0 mm/hr, and 7.8 mg/L, respectively. Of the 65 patients with MPA, 18, 32, and 12 had type 2 diabetes mellitus, hypertension, and dyslipidaemia, respectively. The median circulating CD138 levels were 62.8 ng/mL. Regarding the variables during follow-up, 12 of the 65 patients (18.5%) progressed to a medical status requiring renal replacement therapy over a median ESKD-based follow-up of 24.3 months from the time of MPA diagnosis. Sixty-three patients (96.9%) received glucocorticoids for MPA treatment. The most frequently administered immunosuppressive drugs were cyclophosphamide (66.2%), azathioprine (58.5%), and mycophenolate mofetil (24.6%) (Table 1).

Correlation analysis

At diagnosis, circulating CD138 was significantly correlated with BVAS (r=0.402), FFS (r=0.387), ESR (r=0.495), CRP (r=0.388), white blood cell count (r=0.694), haemoglobin (r=-0.402), blood urea nitrogen (r=0.372), serum creatinine (r=0.362), and serum albumin (r=-0.580) (Table 2).

Cut-off and RR for future progression to ESKD

The AUC of circulating CD138 at diagnosis for future progression to ESKD was 0.709 [95% confidence interval (CI)=0.558, 0.860; p=0.025] in the ROC curve analysis. The optimal cut-off of circulating CD138 for future progression to ESKD was determined to be 73.3 ng/mL, with a sensitivity of 83.3% and specificity of 67.9% (Fig. 1). When patients were divided into two groups according to circulating CD138 ≥73.3 ng/mL, those with circulating CD138 ≥73.3 ng/mL at diagnosis exhibited a higher RR for future progression to ESKD than those with circulating CD138 <73.3 ng/mL at diagnosis (RR=10.588; 95% CI=2.087, 53.721; p=0.002) (Fig. 1).

Comparison of cumulative ESKD-free survival rates

Patients with circulating CD138 ≥73.3 ng/mL at diagnosis exhibited a significantly lower cumulative ESKD-free survival rate than those with circulating CD138 <73.3 ng/mL at diagnosis (p=0.001) (Fig. 2).

Table 2. Correlation Analysis of Circulating CD138 at Diagnosis with Continuous Variables at Diagnosis in Patients with MPA (n=65)

Variables	Univariable	
	r	p
Demographic data		
Age	-0.214	0.086
AAV-specific indices		
BVAS	0.402	0.001
FFS	0.387	0.001
Acute-phase reactants		
ESR	0.495	<0.001
CRP	0.388	0.002
Laboratory results		
White blood cell count	0.694	<0.001
Haemoglobin	-0.402	0.001
Platelet count	0.181	0.156
Blood urea nitrogen	0.372	0.002
Serum creatinine	0.362	0.003
Total serum protein	0.168	0.196
Serum albumin	-0.580	<0.001

MPA, microscopic polyangiitis; ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.
Correlation coefficients (r) were calculated using Pearson's correlation analysis.

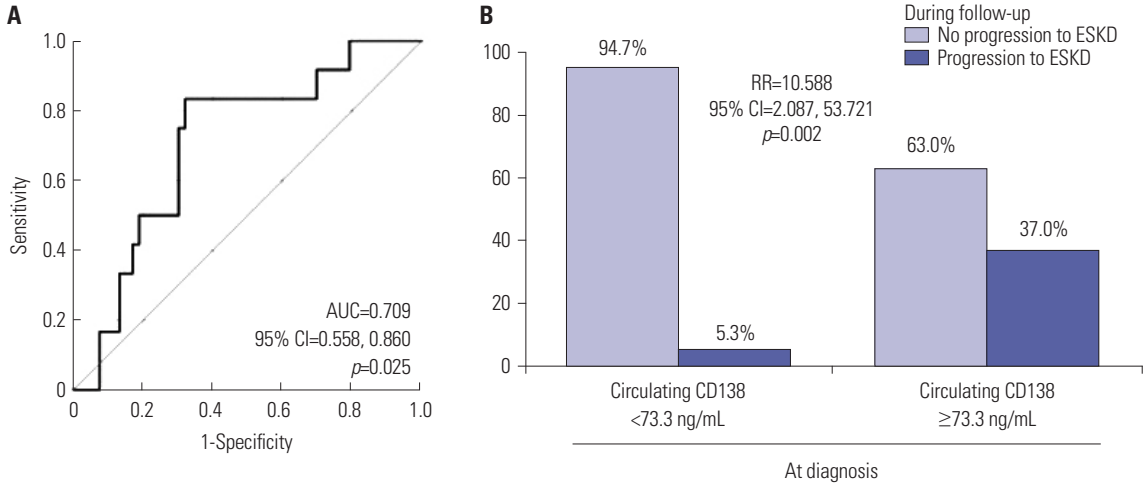

Fig. 1. ROC curve analysis and RR for future progression to ESKD in patients with MPA. (A) The AUC of circulating CD138 for predicting ESKD was statistically significant, and the cut-off value at diagnosis was set at 73.3 ng/mL. (B) The RR for future progression to ESKD in patients with circulating CD138 levels ≥73.3 ng/mL at diagnosis was calculated to be as high as 10.588. ROC, receiver operating characteristic; RR, relative risk; CI, confidence interval; ESKD, end-stage kidney disease; MPA, microscopic polyangiitis; AUC, area under the curve.

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Cox proportional analyses for future progression to ESKD

Cox proportional hazards analyses included only the initial variables at the time of MPA diagnosis, which might be associated with future progression to ESKD. In univariable Cox analysis, BVAS, FFS, serum creatinine, serum albumin, and circulating CD138 levels ≥73.3 ng/mL were significantly associated with future progression to ESKD. In the multivariable Cox analysis, only serum creatinine levels (HR=3.816; 95% CI=1.695, 8.594) were independently associated with future progression to ESKD (Table 3).

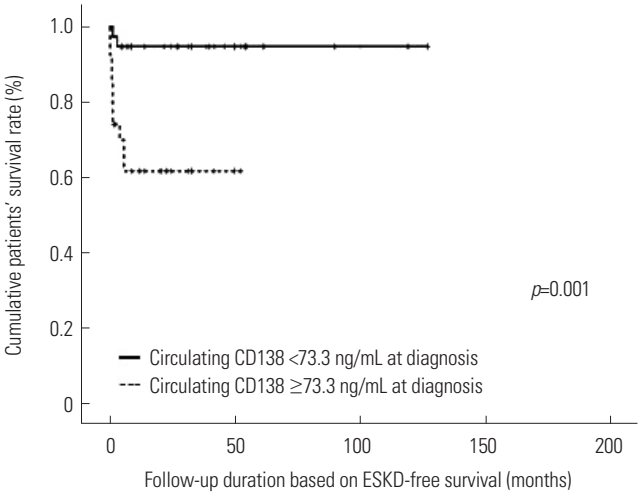

Fig. 2. Comparison of cumulative ESKD-free survival rates in patients with MPA. Patients with circulating CD138 levels ≥73.3 ng/mL at diagnosis exhibited significantly lower cumulative ESKD-free survival rates than those with lower levels. ESKD, end-stage kidney disease; MPA, microscopic polyangiitis.

DISCUSSION

In this study, we investigated the clinical utility of circulating CD138 at diagnosis as a biomarker for predicting future progression to ESKD in patients with MPA and obtained several interesting findings. First, circulating CD138 levels at diagnosis reflected cross-sectional MPA-specific indices such as BVAS and FFS, and the inflammatory burden expressed by ESR, CRP, and serum albumin. Second, circulating CD138 was positively correlated with serum creatinine levels at diagnosis. Third, ROC curve analysis identified circulating CD138 at diagnosis as a significant predictor of future progression to ESKD (AUC=0.709), with an optimal cut-off of 73.3 ng/mL. Patients with CD138 levels ≥73.3 ng/mL had a significantly higher RR (10.588) for progression to ESKD and exhibited duced ESKD-free survival rates compared to those with CD138 levels <73.3 ng/mL. Moreover, when accounting for the time-to-event structure, the time-dependent AUCs for the CD138 cut-off (0.767 at 12 months, 0.811 at 24 months, and 0.849 at 36 months) were consistently higher than the conventional ROC AUC (0.709) reported in our initial analysis (Supplementary Fig. 1, only online). This suggests that the prognostic value of CD138 persists even when accounting for the time-to-event structure of ESKD progression, reinforcing its potential clinical utility as a robust long-term biomarker. Fourth, however, in Cox proportional analyses, CD138 ≥73.3 ng/mL at diagnosis did not independently predict future progression to ESKD, and the predictive potential of CD138 ≥73.3 ng/mL for ESKD could not surpass that of serum creatinine at diagnosis. Therefore, although it is confined to AAV and more supporting evidence is needed, based on these results, we concluded that circulating CD138 measured at the time of MPA diagnosis has clinical utility as a bio-

Table 3. Cox Hazards Model Analyses of Variables at Diagnosis for Future Progression to ESKD during Follow-Up in Patients with MPA

Variables	Univariable			Multivariable (serum CD138 levels)		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.044	0.977, 1.117	0.203			
Female sex	49.924	0.444, 5614.738	0.105			
MPO-ANCA (or P-ANCA) positivity	25.668	0.025, 26636.216	0.360			
PR3-ANCA (or C-ANCA) positivity	0.047	0.000, 244423.112	0.699			
BVAS	1.066	1.001, 1.135	0.048	0.931	0.801, 1.084	0.357
FFS	2.890	1.176, 7.100	0.021	0.353	0.045, 2.760	0.321
Type 2 diabetes mellitus	0.573	0.125, 2.615	0.472			
Hypertension	2.373	0.714, 7.890	0.159			
Dyslipidaemia	1.029	0.225, 4.701	0.970			
White blood cell count	1.054	0.970, 1.146	0.213			
Blood urea nitrogen	1.020	0.997, 1.044	0.083			
Serum creatinine	1.440	1.175, 1.766	<0.001	3.816	1.695, 8.594	0.001
Total serum protein	0.719	0.345, 1.500	0.380			
Serum albumin	0.436	0.193, 0.988	0.047	0.195	0.018, 2.101	0.178
Circulating CD138 levels ≥73.3 ng/mL	8.477	1.854, 38.756	0.006	1.177	0.128, 10.856	0.886

ESKD, end-stage kidney disease; MPA, microscopic polyangiitis; HR, hazard ratio; CI, confidence interval; MPO, myeloperoxidase; ANCA, antineutrophil cytoplasmic antibody; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score.

marker to presume cross-sectional activity and further predict future progression to ESKD in patients with MPA.

To explore the reason why circulating CD138 lost statistical significance in the multivariable model, we hypothesized that this attenuation was due to the inclusion of patients without renal involvement, which resulted in a wide variation in baseline serum creatinine levels. To address this, we conducted a subgroup analysis limited to patients with kidney involvement at diagnosis, defined as a renal BVAS version 3 score ≥2. In this subgroup, only circulating CD138 ≥73.3 ng/mL remained independently associated with progression to ESKD in multivariable analysis (Supplementary Table 1, only online). These results suggest that circulating CD138 may serve as an independent prognostic marker in patients with kidney involvement and further highlight its potential clinical utility beyond traditional activity indices.

Which mechanism measured by circulating CD138 at the time of diagnosis in patients with MPA could serve as a biomarker for predicting future progression to ESKD? We propose the following two hypotheses: the first hypothesis is that circulating CD138 at diagnosis can predict future progression to ESKD by reflecting cross-sectional early renal damage and functional decline.[15] The results of this study showed that circulating CD138 levels at diagnosis were significantly proportional to cross-sectional serum creatinine levels at diagnosis, which is a major predictor of renal replacement therapy initiation.[16] Additionally, circulating CD138 at diagnosis was significantly correlated with the sum of the points assigned to the renal manifestation item of the 9 BVAS items (r=0.400, p=0.001). Furthermore, it was significantly correlated with proteinuria (r=0.422, p<0.001) but not with haematuria. However, it seems difficult to assert the clinical utility of circulating CD138 based solely on this mechanism, reflecting the renal functional decline represented by serum creatinine levels. In particular, in the Cox analysis, circulating CD138 failed to prove non-inferiority compared to serum creatinine in its independent predictive ability for ESKD. In addition, when we compared the AUCs for future progression to ESKD between circulating CD138 and serum creatinine levels at diagnosis using the ROC curve analysis, the AUC of circulating CD138 was lower than that of serum creatinine (Supplementary Fig. 2, only online).

The second hypothesis is that circulating CD138 at diagnosis can predict future progression to ESKD by anticipating a cross-sectional inflammatory burden represented by acute-phase reactants. ESR and CRP levels have been recognised as initial predictors of ESKD in patients with AAV.[17,18] The results of this study revealed that circulating CD138 levels at diagnosis were significantly correlated with cross-sectional ESR and CRP levels at diagnosis. In addition, when the AUCs for future progression to ESKD among circulating CD138, ESR, and CRP levels were compared using the ROC curve analysis, all showed significant AUCs (Supplementary Fig. 3, only online). Therefore, circulating CD138 showed a predictive potential for ESKD, comparable to ESR and CRP levels at diagnosis. Given that serum creatinine levels primarily reflect cross-sectional renal function and the extent of renal damage, their predictive value for future progression to ESKD is limited. In the context of AAV pathophysiology, an advanced inflammatory response, including an increase in the amount and activity of various cytokines or chemokines, precedes or is accompanied by activated neutrophil degranulation, and macrophage infiltration, which directly contribute to the pathogenesis of renal damage.[19,20] Accordingly, we cannot overlook the fact that the burden of inflammation represented by the current ESR or CRP levels may affect renal damage in the present and near future. Therefore, although circulating CD138 at diagnosis failed to show an independent predictive ability for future progression to ESKD compared to serum creatinine at diagnosis, we believe that the clinical utility of circulating CD138 is reasonable in that it may reflect systemic inflammation beyond the kidneys.

Previous studies have demonstrated that soluble CD138 can bind APRIL, thereby promoting B cell differentiation. Additionally, soluble CD138 has been implicated in autoreactive B cell differentiation and autoantibody production in MRL/Lpr mice, suggesting a potential immunogenic role in autoimmune pathology.[1] Given these findings, it is plausible that circulating CD138 may not only serve as a biomarker of disease progression but also actively contribute to the inflammatory milieu in autoimmune diseases. Further investigations are warranted to elucidate whether circulating CD138 exerts immunomodulatory effects by facilitating B cell activation, autoantibody production, or inflammatory signalling cascades within the renal microenvironment. Experimental studies, including in vitro functional assays and in vivo disease models, will be essential to clarify the pathogenic role of CD138 and its potential as a therapeutic target in MPA.

Meanwhile, serum albumin could act as an acute-phase reactant, as well as an indicator closely related to proteinuria in patients with MPA.[21,22] First, as an acute-phase reactant, serum albumin showed strong inverse correlations with ESR (r=-0.688, p<0.001), CRP (r=-0.701, p<0.001), and circulating CD138 (r=-0.580, p<0.001). Second, as an indicator closely related to proteinuria and/or renal function, serum albumin at diagnosis was inversely correlated with serum creatinine (r=-0.257, p=0.045), and the sum of points assigned to a sub-item of proteinuria (r=-0.609, p<0.001). Based on these findings, serum albumin is inferred to be a biomarker that has the advantage of predicting both renal and inflammatory statuses as efficiently as circulating CD138 levels. However, in ROC curve analysis, serum albumin at diagnosis exhibited no significant AUC for future progression to ESKD, unlike circulating CD138 (Supplementary Fig. 4, only online). Therefore, the clinical utility of circulating CD138 may be a unique biomarker for predicting future progression to ESKD in patients with MPA.

In summary, circulating CD138 at diagnosis has clinical utility in predicting future progression to ESKD by assessing cross-

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sectional renal function or damage status, and reflecting the amount and extent of systemic inflammatory burden in the present or near future in patients with MPA. Given its potential to identify high-risk patients who are more likely to require dialysis, incorporating CD138 measurement into the initial workup could provide valuable prognostic insights. In particular, the proposed circulating CD138 cut-off value of 73.3 ng/mL may serve as a useful threshold for risk stratification.

A key strength of this study is that it is the first to demonstrate the clinical usefulness of circulating CD138 at diagnosis for predicting progression to ESKD in patients with MPA. This study has several limitations. First, we did not include a sufficient number of patients in determining whether positive results would be obtained due to the pilot nature of the study. Second, although we selected patients with MPA from a prospective AAV cohort, we conducted this study retrospectively using collected sera as well as clinical data at diagnosis. The retrospective design and the use of data from a single center may limit the generalizability of our findings, as patient characteristics and treatment approaches may vary across institutions and populations. Third, as not all patients had paired blood samples, we could not determine longitudinal alterations in circulating CD138 levels. This limitation restricts our ability to evaluate dynamic changes in CD138 during disease progression and in response to treatment. Fourth, we could not prove the direct effect of circulating CD138 on changes in the number and/or function of plasma cells in the peripheral blood or kidney tissues. We believe that future prospective studies with more patients and paired blood samples will provide more reliable and dynamic information regarding the utility of circulating CD138 levels in patients with MPA.

In conclusion, in the present study, we demonstrated for the first time that circulating CD138 measured at diagnosis has clinical utility as a biomarker for predicting future progression to ESKD in patients with MPA. Additionally, we inferred that circulating CD138 at diagnosis has a unique clinical advantage in predicting future progression to ESKD in patients with MPA, by reflecting not only initial renal dysfunction or damage but also the magnitude and extent of systemic inflammatory burden. However, given that it failed to independently predict progression beyond conventional markers such as serum creatinine in multivariable analysis, further validation in larger, prospective cohorts is warranted.

DATA AVAILABILITY

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jung Yoon Pyo and Sang-Won Lee. Data curation: Sang-Won Lee. Formal analysis: Jung Yoon Pyo. Funding acquisition: Sang-Won Lee. Investigation: Jung Yoon Pyo. Methodology: Jung Yoon Pyo. Project administration: Sang-Won Lee. Resources: Sang-Won Lee. Software: Sang-Won Lee. Supervision: Yong-Beom Park and Sang-Won Lee. Validation: Sang-Won Lee. Visualization: Sang-Won Lee. Writing—original draft: Jung Yoon Pyo. Writing—review & editing: Yong-Beom Park and Sang-Won Lee. Approval of final manuscript: all authors.

ORCID iDs

Jung Yoon Pyo https://orcid.org/0000-0002-1866-6885
Yong-Beom Park https://orcid.org/0000-0003-4695-8620
Sang-Won Lee https://orcid.org/0000-0002-8038-3341

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