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Usefulness of DKK1 in Estimating Vasculitis Activity and End-Stage Kidney Disease in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Patients

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Purpose: To investigate whether serum levels of Dickkopf-related protein-1 (DKK1) are clinically useful in estimating cross-sectional vasculitis activity and predicting future prognosis in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

Materials and Methods: This study included 76 patients with AAV. Their clinical data were retrospectively reviewed and serum DKK1 levels were measured in blood samples collected and stored at diagnosis. At diagnosis, the Birmingham vasculitis activity score (BVAS) and the five-factor score (FFS) were assessed as AAV activity indices, and the erythrocyte sedimentation rate and C-reactive protein (CRP) level were recorded as acute-phase reactants. All-cause mortality and end-stage kidney disease (ESKD) were investigated as poor outcomes during follow-up.

Results: Among the 76 patients with AAV (31 males, and 45 females), the median age was 63.5 years. At diagnosis, serum DKK1 levels were significantly correlated with BVAS, FFS, CRP, serum albumin, and serum creatinine levels. Using receiver operating characteristic curve analysis, the cut-off serum DKK1 level for predicting ESKD was determined to be 3925.0 pg/mL. Patients with serum DKK1 levels ≥3925.0 pg/mL at diagnosis displayed a significantly higher risk of ESKD progression (relative risk 5.357) and exhibited a significantly lower cumulative ESKD-free survival rate during follow-up than those with lower levels.

Conclusion: The present study is the first to demonstrate that serum DKK1 levels at diagnosis are useful in assessing vasculitis activity at diagnosis and predicting future ESKD progression in patients with AAV.

Key Words: DKK1, antineutrophil cytoplasmic antibody, vasculitis, activity, end-stage kidney disease

INTRODUCTION

Dickkopf-related protein (DKK) is a group comprising five secreted glycoproteins, which are characterized by the N-terminal conserved cysteine-rich domains.[1,2] DKK1 is predominantly produced and secreted by osteoblasts and osteocytes and is importantly involved in bone metabolism.[3] Expression of DKK1 is also observed in other tissues, such as female dominant tissues (ovaries and placenta) and kidneys.[4,5] The most common clinical role of DKK1 is to participate in the Wnt signal pathway and further act as an antagonist against Wnt signals. In the absence of Wnt signals, a protein complex consisting of AXIN, casein kinase 1, adenomatous polyposis coli, and glycogen synthase kinase-3β may induce proteasome-mediated degradation of phosphorylated β-catenin and ultimately inhibit the nuclear translocation of β-catenin and its subsequent transcription of downstream gene expression. Conversely, in the presence of Wnt signals, when Wnt binds to both frizzled receptors and lipoprotein receptor-related protein 5 (LRP5), this protein complex involved in β-catenin degradation may lose

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the potential to interfere with intracellular β-catenin signaling and may finally allow target gene expression. When DKK1 binds to LRP5 at this time, it prevents Wnt from binding to LRP5 even though Wnt binds to the frizzled receptor, ultimately turning off Wnt signals and suppressing the transcriptional potential of β-catenin.[6-8] Based on these molecular action mechanisms, to date, the clinical utility of serum DKK1 levels has been reported in patients with various chronic inflammatory diseases and cancers.[9,10]

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is one of the systemic vasculitides affecting small-sized vessels and is characterized by immune deposit-free fibrinoid necrotizing vasculitis.[11] Histologically, according to the presence of granulomatous inflammation and/or eosinophilic extravasation, AAV is divided into three subtypes, microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[11,12] Among major organ involvements of AAV, the kidneys are among the most frequently affected organs along with the skin and lungs: 90%–100% of MPA patients, 50%–80% of GPA patients, and up to 51% of EGPA patients.[13] Accordingly, early recognition of kidney involvement is necessary for a better prognosis, but two major hurdles hinder this: first, a considerable proportion of patients who progress to ESKD show preserved kidney function at AAV onset; second, many patients exhibit no clinical evidence of renal vasculitis at the time of ESKD diagnosis.[14] Therefore, it may be quite difficult to predict the progression of ESKD using only indicators reflecting general renal function or the degree of vascular inflammation. Given that AAV shares immunological pathophysiology with chronic inflammatory diseases and cancers, and that DKK1 has profibrotic properties in progressive chronic kidney disease,[5] it is conceivable that serum DKK1 levels may play similar clinical roles in patients with AAV; however, no published study has addressed this to date. Hence, in the present study, we investigated whether serum DKK1 levels could have clinical usefulness in estimating cross-sectional vasculitis activity and in predicting future prognosis in patients with AAV.

MATERIALS AND METHODS

Patients

We randomly selected 80 patients with AAV from a single-centre cohort of Korean patients with AAV and screened their medical records retrospectively according to the inclusion and exclusion criteria of the present study. The inclusion criteria were as follows: the first was the diagnosis of AAV according to the two principles including both the classification algorithm for AAV proposed by the European Medicine Agency in 2007 and the revised nomenclature of vasculitides suggested by the Chapel Hill Consensus Conference in 2012[11,12]; the second was the reclassification as AAV according to the newly proposed 2022 American College of Medicine and the European Alliance of Associations for Rheumatology classification criteria [the 2022 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria] for AAV[15-18]; the third was the diagnosis at this tertiary university hospital by rheumatologists; the fourth was the presence of available medical records sufficient to collect not only clinical data at the time of diagnosis but also those during the follow-up period; the fifth was the follow-up of ≥6 months. The exclusion criteria were as follows: the first was the absence of serious medical conditions to mimic AAV and confound its classification at AAV diagnosis[15-17]; and the second was no exposure to immunosuppressive drugs for AAV treatment within 4 weeks before AAV diagnosis. Additionally, all patients provided written informed consent upon cohort enrolment and supplied blood samples (sera) that were collected at diagnosis and stored until the time of analysis. Of the 80 patients, two were excluded because of insufficient detailed clinical data during follow-up. Two others were excluded due to unavailable blood samples. The remaining 76 patients were included and analysed. The present study was approved by the Institutional Review Board (IRB) of Severance Hospital, Seoul, Republic of Korea (IRB number 4-2016-0901). All patients in this study provided written informed consent upon enrolment in the cohort of AAV at diagnosis and blood sampling. The additional written informed consent for this study was waived by the IRB if it was obtained at the time of enrolment in the cohort.

Clinical data at AAV diagnosis

Age, sex, smoking history, and body mass index were collected as demographic data. AAV subtype, ANCA type and positivity, and AAV-specific indices such as the Birmingham vasculitis activity score (BVAS) and five-factor score (FFS) were obtained.[19,20] According to the 2022 ACR/EULAR criteria, ANCA results measured by immunoassays [myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA] and those detected by indirect immunofluorescence assays [perinuclear (P)-ANCA and cytoplasmic (C)-ANCA] were both considered valid.[15-17,21] Type 2 diabetes mellitus, hypertension, and dyslipidaemia were recognised as comorbidities of AAV only when they were diagnosed before AAV diagnosis. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum albumin levels were recorded as acute-phase reactants,[22] and the remaining laboratory results were also collected.

Clinical data during AAV follow-up

In this study, all-cause mortality and end-stage kidney disease (ESKD) were investigated as poor outcomes of AAV. All-cause mortality was defined as death from any aetiology except accidents, whereas ESKD was defined as deterioration of kidney function requiring renal replacement therapy. Only all-cause mortality and ESKD events occurring after AAV diagnosis were considered poor outcomes of AAV. The follow-up dura-

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tion for all-cause mortality was defined as the period from AAV diagnosis to death for deceased patients, whereas for surviving patients it was from AAV diagnosis to the last visit. Similarly, for patients with ESKD, the follow-up duration was from AAV diagnosis to initiation of renal replacement therapy, whereas for those without ESKD it was from AAV diagnosis to the last visit. According to the definitions above, disease duration, overall follow-up duration, and follow-up duration for all-cause mortality were identical in this study. Medications including glucocorticoids and immunosuppressive drugs, which were administered to the patients during AAV follow-up, were also recorded.

Measurement of serum DKK1 levels

According to the protocol of the AAV cohort at this hospital, once written informed consent was provided at diagnosis, whole blood was collected from the patients with their permission. On the same day, sera were isolated immediately from whole blood and stored at -80°C. Serum DKK1 levels were measured in the stored sera collected from immunosuppressive-naïve patients with AAV at the time of diagnosis using enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, USA).

Statistical analyses

All statistical analyses were performed using SPSS version 26 (IBM Corporation, Armonk, NY, USA) for Windows (Microsoft Corporation, Redmond, WA, USA). Continuous and categorical variables were expressed as medians (25th–75th percentiles) and numbers (percentages). Correlation coefficients (r) between the two variables were determined using Pearson correlation analysis. Significant differences between the two categorical variables were analysed using chi-square and Fisher's exact tests. Significant differences between two continuous variables were compared using the Mann–Whitney U test. A significant area under the curve (AUC) was determined using receiver operating characteristic (ROC) curve analysis. The cut-off was extrapolated by ROC curve analysis as the point with the maximum sum of sensitivity and specificity; the relative risk (RR) of this cut-off for all-cause mortality was analysed using contingency tables and chi-square test. A comparison of the cumulative survival rates between the two groups was performed using Kaplan–Meier survival analysis with the log-rank test. A multivariable Cox proportional hazard model including variables with $p<0.05$ in univariable analysis was performed to obtain hazard ratios (HRs) for each poor outcome of AAV during follow-up. $p<0.05$ was considered statistically significant.

RESULTS

Clinical data at AAV diagnosis

Among the 76 patients (31 males, 45 females) with AAV (37 with MPA, 22 with GPA, and 17 with EGPA), the median age was 63.5 years. MPO-ANCA (or P-ANCA) and PR3-ANCA (or C-ANCA)

Table 1. Clinical Data at Diagnosis and During Follow-Up in Patients with AAV (n=76)

Variables	Values
At diagnosis	
Demographic data	
Age (yr)	63.5 (52.3–74.0)
Sex	
Male	31 (40.8)
Female	45 (59.2)
Ex-smoker	3 (3.9)
Body mass index (kg/m^2)	22.5 (21.1–24.8)
AAV subtype	
MPA	37 (48.7)
GPA	22 (28.9)
EGPA	17 (22.4)
ANCA positivity	
MPO-ANCA (or P-ANCA) positive	43 (56.6)
PR3-ANCA (or C-ANCA) positive	10 (13.2)
Both ANCA positive	3 (3.9)
ANCA negative	26 (34.2)
AAV-specific indices	
BVAS	5 (3.0–17.0)
FFS	0 (0–1.0)
Systemic manifestation according to the items of BVAS	
General manifestations	14 (18.4)
Cutaneous manifestations	12 (15.8)
Mucous/ocular manifestations	6 (7.9)
Ear, nose, and throat manifestations	39 (51.3)
Pulmonary manifestations	46 (60.5)
Cardiovascular manifestations	9 (11.8)
Gastrointestinal manifestations	0 (0)
Renal manifestations	38 (50.0)
Central/peripheral nervous system manifestations	27 (35.5)
Comorbidities	
Type 2 diabetes mellitus	17 (22.4)
Hypertension	25 (32.9)
Dyslipidaemia	13 (17.1)
Acute-phase reactants	
ESR (mm/hr)	17.5 (7.0–68.0)
CRP (mg/L)	3.0 (0.8–16.0)
Laboratory results	
White blood cell count (/mm^3)	7510.0 (5937.5–10882.5)
Haemoglobin (g/dL)	12.5 (10.2–13.7)
Platelet count (×1000/mm^3)	240.0 (190.0–350.0)
Blood urea nitrogen (mg/dL)	19.8 (14.0–29.5)
Serum creatinine (mg/dL)	0.8 (0.6–1.6)
Total serum protein (g/dL)	6.8 (6.4–7.3)
Serum albumin (g/dL)	4.2 (3.8–4.4)
C3 (mg/dL)	112.8 (97.5–124.8)
C4 (mg/dL)	24.9 (20.2–30.9)
Serum DKK1 levels (pg/mL)	4010.0 (3354.5–4837.8)

Table 1. Clinical Data at Diagnosis and During Follow-Up in Patients with AAV (n=76) (continued)

Variables	Values
During follow-up	
Poor outcome	
All-cause mortality	6 (7.9)
ESKD	18 (23.7)
Follow-up duration based on each pooroutcome (months)	
All-cause mortality	26.7 (11.9–44.7)
ESKD	26.4 (8.7–44.7)
Medications	
Glucocorticoids	75 (98.7)
Cyclophosphamide	50 (65.8)
Rituximab	14 (18.4)
Mycophenolate mofetil	17 (22.4)
Azathioprine	47 (61.8)
Tacrolimus	7 (9.2)
Methotrexate	3 (3.9)

ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic GPA; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; C3, complement 3; C4, complement 4; DKK1, Dickkopf-related protein-1; ESKD, end-stage kidney disease.
Values are expressed as a median (25th–75th percentile) or a number (%).

were detected in 43 and 10 patients, respectively. The median BVAS and FFS were 5 and 0, respectively; the median ESR was 17.5 mm/hr, and the median CRP was 3.0 mg/L. The most frequently observed systemic manifestation was lung involvement (60.5%), followed by ear, nose, and throat involvement (51.3%) and renal (50.0%) involvement. The median serum DKK1 level was 4010.0 pg/mL. The remaining laboratory results are presented in Table 1.

Clinical data during AAV follow-up

Among the 76 patients with AAV, 6 died and 18 patients progressed to ESKD during the disease course. The median follow-up durations for all-cause mortality and ESKD were 26.7 months and 26.4 months, respectively. Of the 76 patients, 75 (98.7%) received glucocorticoids. Among immunosuppressive drugs, cyclophosphamide (65.8%) was the most frequently administered, followed by azathioprine (61.8%) (Table 1).

Correlation analysis

At the time of AAV diagnosis, serum DKK1 levels were positively correlated with BVAS (r=0.278, p=0.015), FFS (r=0.236, p=0.040), CRP (r=0.280, p=0.017), platelet count (r=0.261, p=0.024), and serum creatinine (r=0.343, p=0.002), and inversely correlated with haemoglobin (r=-0.342, p=0.002) and serum albumin (r=-0.315, p=0.006). Serum DKK1 levels tended to be correlated with ESR and total protein but did not reach statistical significance (Table 2).

Table 2. Correlation of Serum DKK1 Levels and Other Continuous Variables at Diagnosis in Patients with AAV

Variables	Correlation coefficient (r)	p
Demographic data		
Age	-0.028	0.810
Body mass index	-0.080	0.491
AAV-specific indices		
BVAS	0.278	0.015
FFS	0.236	0.040
Acute-phase reactants		
ESR	0.220	0.068
CRP	0.280	0.017
Laboratory results		
White blood cell count	0.187	0.106
Haemoglobin	-0.342	0.002
Platelet count	0.261	0.024
Blood urea nitrogen	0.143	0.218
Serum creatinine	0.343	0.002
Total serum protein	-0.230	0.050
Serum albumin	-0.315	0.006
C3	0.011	0.929
C4	0.192	0.108

DKK1, Dickkopf-related protein-1; 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; C3, complement 3; C4, complement 4.

Comparative analysis

Among variables at AAV diagnosis, serum DKK1 levels differed between male and female patients. Female patients exhibited significantly higher serum DKK1 levels than males (4235.0 pg/mL vs. 3929.0 pg/mL, p=0.034). As serum DKK1 levels may be influenced by age as well as sex, ages were compared between the two sex groups. Female patients tended to be older than male patients (70.0 years vs. 61.0 years); however, no significant difference in age was observed between the two groups (p=0.271). Among poor outcomes during AAV follow-up, patients with ESKD exhibited significantly elevated serum DKK1 levels at diagnosis compared to those without (4625.0 pg/mL vs. 3844.5 pg/mL, p=0.038) (Table 3).

ROC curve analysis and RR for future ESKD progression

Using ROC curve analysis, the AUC of serum DKK1 levels at diagnosis for ESKD progression during AAV follow-up was significant [AUC 0.662, 95% confidence interval (CI) 0.513, 0.811, p=0.038]. The optimal cut-off serum DKK1 level was determined to be 3925.0 pg/mL, with sensitivity and specificity of 83.3% and 51.7%, respectively (Fig. 1A). When patients were divided into two groups according to serum DKK1 levels of 3925.0 pg/mL, ESKD progression occurred more frequently in patients with serum DKK1 levels ≥3925.0 pg/mL than those with serum DKK1 levels <3925.0 pg/mL at AAV diagnosis. Additionally, patients with serum DKK1 levels ≥3925.0 pg/mL

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showed a significantly higher RR for ESKD progression than those with serum DKK1 levels <3925.0 pg/mL (RR 5.357, 95% CI 1.399, 20.507, p=0.013) (Fig. 1B). On the other hand, no significant AUC for all-cause mortality was obtained by ROC curve analysis of serum DKK1 levels at diagnosis.

Table 3. Comparison of Serum DKK1 Levels According to Categorical Variables in Patients with AAV

Variables	Absence (median, pg/mL)	Presence (median, pg/mL)	p
At diagnosis			
Demographic data			
Sex	Male 3929.0	Female 4235.0	0.034
AAV subtypes			
MPA vs. GPA	3637.0	4376.0	0.106
GPA vs. EGPA	4376.0	4235.0	0.515
MPA vs. EGPA	3637.0	4235.0	0.434
ANCA positivity			
MPO-ANCA (or P-ANCA) positive	4382.0	3760.0	0.253
PR3-ANCA (or C-ANCA) positive	4009.0	4171.5	0.951
Comorbidities			
Type 2 diabetes mellitus	3981.0	4192.0	0.965
Hypertension	4039.0	3979.0	0.847
Dyslipidaemia	4039.0	3981.0	0.644
During follow-up			
Poor outcome			
All-cause mortality	3972.5	4976.0	0.184
ESKD	3844.5	4625.0	0.038

DKK1, Dickkopf-related protein-1; ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic GPA; MPO, myeloperoxidase; P, perinuclear; PR3, proteinase 3; C, cytoplasmic; ESKD, end-stage kidney disease.

Comparison of cumulative ESKD-free survival rates

Patients with serum DKK1 levels ≥3925.0 pg/mL at diagnosis exhibited a significantly lower cumulative ESKD-free survival rate than those with serum DKK1 levels <3925.0 pg/mL (Fig. 2).

DISCUSSION

This study investigated the clinical utility of serum DKK1 levels in immunosuppressive drug-naïve AAV patients clinical data and serum samples collected at diagnosis and yielded several notable findings. First, at AAV diagnosis, serum DKK1 levels were significantly correlated with BVAS and FFS as AAV-specific indices and CRP, haemoglobin, and serum albumin as an acute-

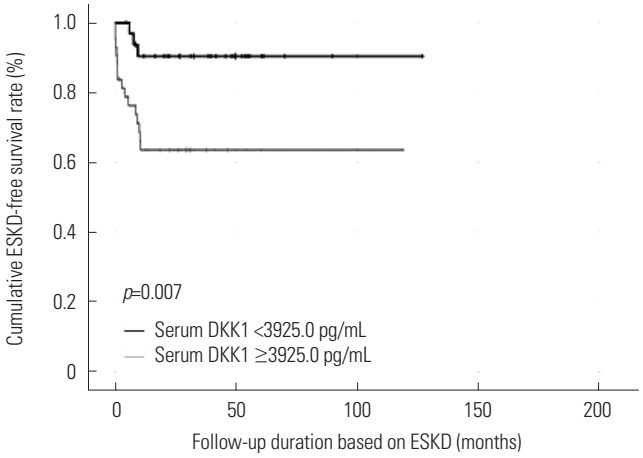

Fig. 2. Comparison of cumulative ESKD-free survival rates in patients with AAV. Serum DKK1 levels ≥3925.0 pg/mL at diagnosis exhibited a significantly reduced cumulative ESKD-free survival rate compared to serum DKK1 levels <3925.0 pg/mL. ESKD, end-stage kidney disease; AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; DKK1, Dickkopf-related protein 1.

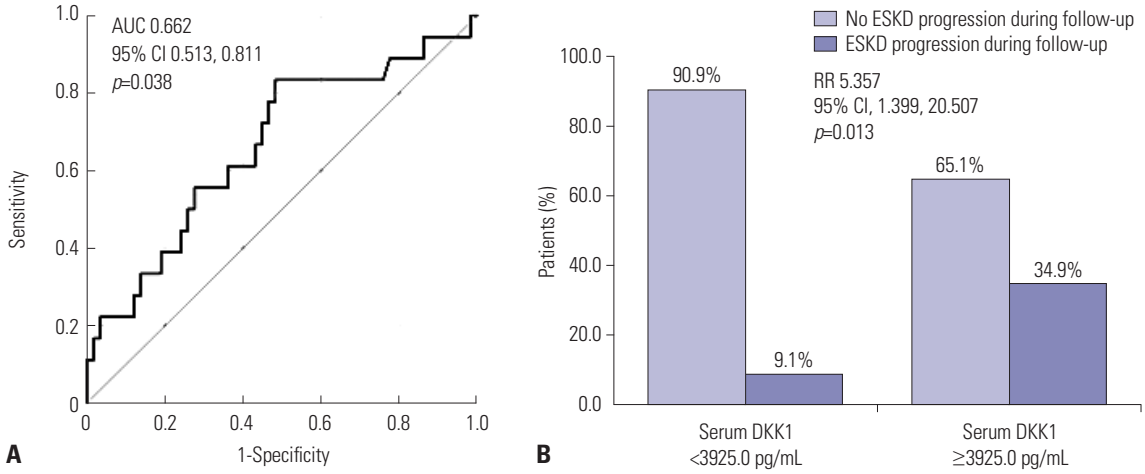

Fig. 1. ROC curve analysis and RR for future ESKD progression in patients with AAV. (A) Cut-off of serum DKK1 levels at diagnosis was set at 3925.0 pg/mL. (B) RR of serum DKK1 levels ≥3925.0 pg/mL at diagnosis for predicting future ESKD progression was calculated as 5.357. ROC, receiver operating characteristic; RR, relative risk; ESKD, end-stage kidney disease; AAV, ANCA-associated vasculitis; ANCA, antineutrophil cytoplasmic antibody; DKK1, Dickkopf-related protein 1; AUC, area under the curve; CI, confidence interval.

phase reactant. Additionally, a significant correlation between serum DKK1 levels and serum creatinine was also observed. Second, at AAV diagnosis, serum DKK1 levels were higher in female patients than in male patients, and higher in those who progressed to ESKD than in those who did not. Third, at AAV diagnosis, patients with serum DKK1 levels ≥3925.0 pg/mL, which was determined as the optimal cut-off for future ESKD progression in ROC curve analysis, showed a significantly higher risk (RR 5.357) of ESKD progression than those with lower levels. Fourth, in Kaplan–Meier survival analysis, patients with serum DKK1 levels ≥3925.0 pg/mL at diagnosis exhibited a significantly lower cumulative ESKD-free survival rate than those with lower levels. Summarizing these results, we conclude that this study is the first to demonstrate the usefulness of serum DKK1 levels in estimating cross-sectional activity, extent of inflammation, and degree of kidney involvement and in predicting ESKD progression during follow-up in patients with AAV.

How could serum DKK1 levels at diagnosis potentially predict ESKD progression in patients with AAV? We propose two mechanisms: kidney-dependent and kidney-nonspecific. First, in the kidney-dependent mechanism at diagnosis, serum DKK1 levels were positively correlated with serum creatinine, a major risk factor for ESKD progression.[23,24] Additionally, among the nine BVAS systemic items at diagnosis, serum DKK1 levels correlated only with the renal manifestation item (r=0.324, p=0.004). Furthermore, they were also positively correlated with the subitems of renal manifestation: proteinuria (r=0.270, p=0.018) and haematuria (r=0.411, p<0.001) (Supplementary Table 1, only online). Therefore, serum DKK1 levels may reflect the extent of renal-specific vasculitis and thus can predict future ESKD progression. However, this inference is a hypothesis limited to this study and is not supported by direct renal cell–level metabolic mechanisms or histological evidence.

Second, in the kidney-nonspecific (systemic inflammation–related) mechanism at diagnosis, serum DKK1 levels correlated with AAV-specific indices (BVAS and FFS)[19,20] and with acute-phase reactants (CRP, haemoglobin, and serum albumin).[22] In addition, among these five variables, serum creatinine exhibited significant correlations with FFS (r=0.624, p<0.001), CRP (r=0.569, p<0.001, haemoglobin (r=-0.455, p<0.001), and serum albumin (r=-0.375, p=0.001). These findings imply that the systemic inflammation-related manner may also indirectly reflect the deterioration in kidney function. Therefore, serum DKK1 levels may indirectly estimate kidney function decline by reflecting systemic inflammation burden and thus predict future ESKD progression.

What immunological mechanisms could enable serum DKK1 levels to predict future ESKD progression in patients with AAV? A previous study demonstrated that increased serum DKK1 levels can notably predict faster ESKD progression in patients with advanced chronic kidney disease.[5] However, direct supporting evidence regarding this issue is scarce. Studies on the clinical role of DKK1 have focused on bone metabolism and cancer immunology,[12,25] with little progress in kidney diseases. Nonetheless, we believe that serum DKK1 levels have more advantages over serum creatinine in anticipating future ESKD progression and provide four hypotheses. The first hypothesis is that serum DKK1 levels may be more sensitive for recognising the possibility of future ESKD progression than serum creatinine itself. In a cross-sectional ROC analysis comparing AUCs for future ESKD progression, serum DKK1 (AUC 0.662, 95% CI 0.513, 0.811, p=0.038) outperformed serum creatinine (AUC 0.566, 95% CI 0.391, 0.741, p=0.399) (Supplementary Fig. 1, only online).

The second hypothesis is that serum DKK1 levels may be a more comprehensive predictor for future ESKD progression than serum creatinine itself. Unlike serum creatinine, serum DKK1 levels are believed to play a more dynamic role in that they reflect kidney-nonspecific inflammatory parameters such as CRP, and serum albumin, extensively reflecting inflammation in systemic vasculitis rather than being a simple link between initial renal dysfunction and future ESKD progression.[26] This hypothesis would be a more vasculitis pathology-friendly analysis. The third hypothesis is that serum DKK1 levels may better detect ongoing renal abnormalities affected by AAV than serum creatinine itself. In this study, serum DKK1 levels were significantly correlated with proteinuria as well as haematuria. Furthermore, the proportionality with haematuria was greater than with proteinuria. Given that proteinuria and haematuria often occur before remarkable renal dysfunction and that particularly, haematuria is a major predictor of renal relapse after remission in patients with AAV,[27,28] serum DKK1 levels are believed to have merit in detecting early renal alterations.

The last hypothesis is that serum DKK1 levels can improve the predictive specificity for kidney-confined and systemic inflammation compared with serum creatinine. DKK1 is produced dependent on or independent of canonical Wnt signal pathways. In Wnt signal pathway-dependent DKK1 production, DKK1 is one of the target genes of β-catenin, and Wnt signals increase DKK1 production. The produced DKK1 inhibits the Wnt signalling pathway, ultimately limiting further DKK1 production (negative feedback). Conversely, in terms of the Wnt signal pathway-independent DKK1 production, the axis of DKK1 and cytoskeleton associated protein 4 (CKAP4) initiates phosphoinositide 3-kinase-mediated extracellular signal-regulated kinase and protein kinase B (also known as Akt) activation, which induces Forkhead box protein M1 (FOXM1) expression, which subsequently activates DKK1 expression. The produced DKK1 also amplifies the DKK1–CKAP4 axis and further enhances DKK1 production (positive feedback).[6-8] Therefore, these mechanisms imply that DKK1 production can play diverse disease-specific roles in various diseases, and DKK1 secretion to the blood circulation (serum DKK1 levels) may vary with disease activity or course, even within the same disease. Particularly, the positive feedback of DKK1 production can amplify its serum levels via the DKK1-CKAP4-FOXM1 axis and ultimately

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improve the sensitivity of serum DKK1 levels as a biomarker for estimating cross-sectional activity and predicting future ESKD progression in patients with AAV.

To minimise the influence of various confounding variables included in this study, we conducted univariable and multivariable Cox proportional hazards analyses of variables at diagnosis for progression to ESKD in patients with AAV. In univariable Cox analysis, female sex, ESR, CRP, haemoglobin, serum creatinine, and C3 levels at diagnosis were significantly associated with progression to ESKD during follow-up. Both serum DKK1 levels and serum DKK1 ≥3925.0 pg/mL at diagnosis were also significantly associated with ESKD progression in patients with AAV. In multivariable Cox analysis including serum DKK1 levels, female sex (HR 5.151, 95% CI 1.019, 26.048), ESR (HR 1.023, 95% CI 1.002, 1.045), and serum creatinine (HR 1.990, 95% CI 1.013, 3.910) at diagnosis were notably associated with progression to ESKD. However, no independent association between serum DKK1 levels and ESKD progression was observed. Similarly, in multivariable Cox analysis using serum DKK1 ≥3925.0 pg/mL, female sex (HR 6.111, 95% CI 1.215, 30.733), ESR (HR 1.022, 95% CI 1.001, 1.045), and serum creatinine (HR 2.109, 95% CI 1.200, 3.708) at diagnosis were significantly associated with progression to ESKD. Unlike continuous serum DKK1 levels, serum DKK1 ≥3925.0 pg/mL at diagnosis tended to be associated with ESKD progression; however, this did not reach statistical significance (HR 4.059, p=0.053) (Supplementary Table 2, only online). Therefore, serum DKK1 ≥3925.0 pg/mL at diagnosis showed a trend toward association with ESKD progression, but its significance did not exceed that of female sex, ESR, and serum creatinine at diagnosis.

Based on serum DKK1 ≥3925.0 pg/mL, we divided patients into two groups and compared variables between them. Among these variables, BVAS, white blood cell count, platelet count, and haemoglobin differed significantly between the two groups. Particularly, as was expected, patients with serum DKK1 ≥3925.0 pg/mL exhibited a significantly higher frequency of ESKD during follow-up than those without (34.9% vs. 9.1%, p=0.013). However, no significant difference in serum creatinine was observed between the two groups (Supplementary Table 3, only online). The fact that serum creatinine, which is closely related to ESKD, did not differ between groups defined by the serum DKK1 cut-off supports our proposed kidney-dependent and kidney-nonspecific mechanisms.

The advantage of this study was that it is the first to demonstrate the clinical potential of serum DKK1 levels at diagnosis for predicting progression to ESKD during follow-up in patients with AAV. Another advantage is that serum DKK1 levels were measured in sera collected at diagnosis before exposure to glucocorticoids or immunosuppressive drugs, thereby minimizing medication effects on DKK1 concentration.

However, the present study has several limitations. First, despite measuring serum DKK1 in samples collected at diagnosis and using clinical data through the last visit, this study was retrospective. Thus, it did not have the advantages of a purely prospective study and could not overcome the inherent limitations of a retrospective study. Second, additional disadvantages of the retrospective study design pattern were that no systemic complications of AAV other than all-cause mortality or ESKD could have been investigated and we could not provide serial values of BVAS and FFS and their changes during follow-up. Third, although a few previous studies have suggested a role of DKK1 in the pathogenesis of chronic kidney disease or ESKD as a profibrotic mediator,[5,29] this study could not provide direct evidence for the contribution of DKK1 to the pathogenesis of ESKD in patients with AAV. Additionally, if we had identified differences in serum DKK1 levels according to the histological classification of the kidneys, we could have provided relatively direct supporting evidence on the mechanism for predicting ESKD progression. However, due to the limitation of this retrospective study design without reports on renal histological classification, we could not compare serum DKK1 levels among the four renal histological classes. Fourth, since this study included clinical data on only DM, hypertension, and dyslipidaemia as comorbidities at diagnosis, it could not provide sufficient information on the wider range of medical conditions at diagnosis that may affect the progression to ESKD. Last, the most critical issue of this study, which should be improved in the next study, was that the number of patients in this single-centre cohort study was not large enough to generalise the results and apply them to AAV patients in other cohorts immediately. Nevertheless, we believe that a future prospective study with more patients alongside healthy controls or patients with other chronic diseases and the repetitive assessment of AAV-specific indices and serial measurement of serum DKK1 levels will overcome these limitations and may clarify the clinical utility of serum DKK1 levels in patients with AAV.

In conclusion, the present study is the first to demonstrate the clinical usefulness of serum DKK1 levels at diagnosis in estimating cross-sectional vasculitis activity at diagnosis and predicting the possibility of future ESKD progression in patients with AAV.

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