



Characteristics of glomerulonephritis with dominant C1q precipitation compared to corresponding glomerulonephritis without C1q staining on immunofluorescent examination

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Background: The clinical significance and renal outcomes of C1q nephropathy (C1qN) are unclear; therefore, the implications of C1qN as a new pathological entity are uncertain. We compared the clinical characteristics of glomerulonephritis reclassified into cases that meet the definition of C1qN and glomerulonephritis not included in the definition of C1qN.

Methods: In total, 21,697 patients who underwent native kidney biopsy at 18 hospitals throughout Korea between 1979 and 2018 were retrospectively enrolled. A total of 77 patients were selected from the group that met the definition of C1qN after reclassification; however, six patients were excluded because of secondary systemic disease. Characteristics of pathological findings classified into C1qN, without C1q stain, and with nondominant C1q stain that did not fulfill the criteria for C1qN were compared.

Results: No differences in clinicopathological findings and incidence of ESRD were evident (matched by age and sex) between glomerulonephritis cases reclassified into the group that met the definition of C1qN and those without C1q staining. Decreased proteinuria in patients with membranous nephropathies reclassified into the group that met the definition of C1qN was the only significant finding. Immunoglobulins showed higher intensity on immunofluorescence staining of the group that met the definition of C1qN. Additionally, C3 intensity was higher in reclassified immunoglobulin A nephropathy and membranous nephropathies.

Conclusion: Overall, reclassification into the group that met the definition of C1qN did not indicate a different clinicopathological identity. C1q activation and presumed classical complement pathway activation in kidney tissues in C1qN could not be confirmed. Hence, further studies are needed.

Keywords: Biopsy, Classical complement pathway, Complement C1q, Glomerulonephritis

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Introduction

C1q nephropathy (C1qN), proposed by Jennette and Hipp in 1985 [1], is defined as renal mesangium with dominant or codominant C1q deposits and the absence of clinicopathological features of systemic lupus erythematosus (SLE) [1]. C1qN exhibits various clinical symptoms, including mild proteinuria with or without hematuria, nephrotic and nephritic syndromes, recurrent gross hematuria, acute renal injury, and rapidly progressive glomerulonephritis (GN), and it is refractory to steroid therapy [2–6]. Diagnosis of C1qN is based on histopathology and renal outcomes are dependent on clinical and histologic factors [7]. However, due to the heterogeneity of these factors, renal outcomes have been inconsistently reported.

Although C1qN was defined 30 years ago, the significance of C1q deposits in GN is still poorly understood, and whether C1qN is a distinct clinicopathological entity or another glomerular disease variant remains controversial [7–9]. C1q deposits occur due to classical pathway activation that begins after C1q binds to immune complexes or charged molecules [10–12]. Since C1q deposits (other than C1qN) are not a diagnostic marker, they have received little attention. Immunoglobulin A nephropathy (IgAN) is important for component activation through the alternative or lectin pathway. However, the deposits of C1q related to the classical pathway may be associated with poor renal outcomes in IgAN [13,14]. The prevalence of IgAN is high in Asian countries, including Korea; therefore, investigating the significance of C1q deposits in GN is vital for developing optimal treatment protocols and identifying prognostic indicator for accurate differential diagnosis of C1qN and other renal diseases. However, different renal outcomes based on C1q deposits have been reported [13–21]; therefore, it is necessary to validate the implication of C1q deposits in GN.

This multicenter cohort study compares clinicopathological findings and renal outcomes between cases, reclassified as per the current diagnostic criteria of C1qN, and existing GNs, before and after matching by age and sex. Additionally, we analyzed the clinicopathologic characteristics of the reclassified group that met the definition of C1qN and investigated risk factors of end-stage renal disease (ESRD).

Methods

This study was conducted in accordance with the Declaration of Helsinki of 1975, as revised in 2013. The study protocol was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (No. B-1707/408-106) and the 17 other participating hospitals. Written consent was waived by the IRB because of the retrospective nature of the study, and all data were fully anonymized before access by the researchers.

Patients and clinical parameters

A total of 21,697 patients who underwent ultrasonography-guided percutaneous native kidney biopsy at 18 hospitals throughout Korea, between 1979 and 2018, were retrospectively enrolled. The biopsy results were interpreted by the respective in-house renal pathologists. The clinical data at the time of biopsy and the last follow-up were queried into the respective hospital information systems (HIS) using the primary inputs of the patients' identification number and date of renal biopsy. Five trained research nurses documented the predefined parameters on a database file template, based on the queried information, and one of the nephrologists reporting this study curated the data for analysis. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease and height-independent equations for adults and children, respectively. Hypertension was physician-diagnosed or defined as systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg or undergoing antihypertensive therapy. Diabetes mellitus (DM) was physician-diagnosed or defined as a random glucose level ≥ 200 mg/dL, hemoglobin A1c $\geq 6.5\%$, or undergoing antidiabetic therapy. Malignancy was defined based on the International Classification of Diseases, 10th Revision codes. The data on final outcomes, incidences of ESRD, and mortality were gathered from the respective hospital's HIS, the ESRD registry of the Korean Society of Nephrology (started in 1980), and Statistics of Korea, and were unified based on Korean ethnicity. The follow-up duration was 69.1 ± 67.8 and 77.9 ± 65.5 months for ESRD and mortality, respectively.

Pathologic diagnosis

The findings and diagnosis by the pathologist of each hospital were applied. All pathologic diagnoses were included to describe the overall trends in the results of renal biopsies. A total of 485 patients were excluded as follows: 191 were diagnosed with cancer, 78 underwent biopsy of a transplanted kidney, two underwent biopsy for kidney donation, and 214 had inadequate biopsy tissue for diagnosis. Finally, 21,212 patients were enrolled. For the purpose of this study, C1qN definition was based on Jennette and Falk's criteria [22], also adopted by another study [8], as follows: 1) presence of $\geq 2+$ C1q in the mesangium on immunofluorescence, predominant or codominant C1q staining (IF); 2) corresponding mesangial or para-mesangial electron-dense deposits on electron microscopy (EM); and 3) lack of clinical and pathological evidence of SLE or type 1 membranoproliferative GN. Based on the earlier reported light microscopy (LM) types of C1qN [23], the pathology was grouped as follows: focal segmental glomerulosclerosis (FSGS), if glomerular segmental sclerosis was observed; proliferative GN (PGN), if mesangial or endothelial proliferation without segmental sclerosis was observed; and minimal change disease (MCD) for pathology not included in FSGS or PGN. Among 21,212 patients, 77 were selected. However, four patients with renal amyloidosis, one with Henoch-Schönlein nephritis and systemic vasculitis, and one with myeloma cast nephropathy were excluded. Finally, 71 patients were classified into a group that met the definition of C1qN (Fig. 1), and the characteristics of cases reclassified into this group were compared with those not included in C1qN.

Renal pathology

Based on the methods of renal pathological evaluation described earlier [15], all biopsies were evaluated using appropriate standards, including hematoxylin and eosin, periodic acid-Schiff, Masson trichrome, and periodic acid methenamine silver stains for LM, IF staining using antibodies against IgA, IgG, IgM, C3, C1q, and kappa and lambda light chains, and EM. Renal changes, including glomerular size, mesangial matrix and cellularity, tubular atrophy, interstitial inflammation, and interstitial fibrosis, were semiquantitatively assessed. Scores ranged from normal to

severe (absence of the lesion; mild changes: lesion present in $<25\%$; moderate changes, lesion present in $25\%–50\%$; and severe changes, lesion present in $\geq 50\%$ of the tissues). The lesions were grouped as normal to mild and moderate to severe. Additionally, atherosclerosis of the renal arterioles was assessed. Pathologists evaluated the IF staining to determine the presence of linear, granular, peripheral, and mesangial deposits in the glomerulus for the IgA, IgG, IgM, C3, C1q, fibrinogen, kappa chain, and lambda chain; these were reported semiquantitatively as negative, trace, and 1–4 positive. The results were numerically converted as follows: negative, 0 points; trace, 0.5 points; and 1–4 positive, 1–4 points. Electron-dense deposits on EM were identified as present or absent, and podocyte effacement was grouped as normal, focal (present in $<50\%$ of tissue) and diffuse lesions (present in $\geq 50\%$ of tissue).

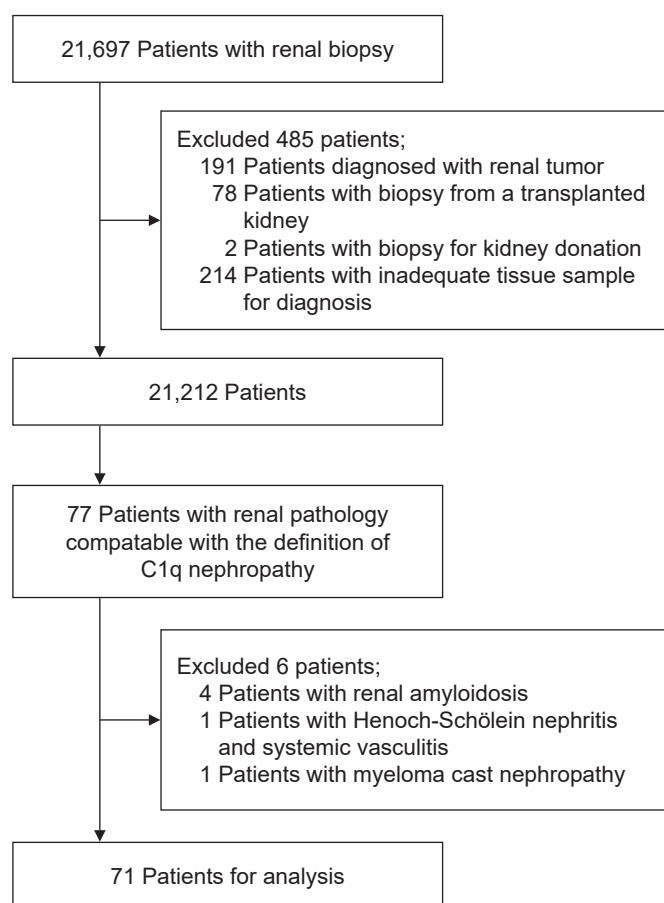


Figure 1. Selection of patients.

Statistical analysis

All analyses were performed using IBM SPSS version 25.0 (IBM Corp.). Descriptive statistics are reported as mean $\pm$ standard deviation for continuous variables or frequency for categorical variables. Differences were analyzed in continuous variables by the Mann-Whitney U test or Kruskal-Wallis test contingent on the number of subgroups, and in categorical variables by the Pearson chi-square test or Fischer exact test contingent on the number of variables. The cumulative incidences of ESRD or mortality by log-rank test were compared between groups and poor risk factors for incident ESRD were selected by the Cox proportional hazard model, adjusted by the related factors. Two-sided p-values of 0.05 were considered to indicate statistical significance.

Results

Characteristics of C1q nephropathy at renal biopsy

The characteristics of reclassified cases that met the definition of C1qN are presented in [Supplementary Table 1](#) (available online); these were compared among groups classified based on the type of LM investigation results obtained from renal biopsy ([Table 1](#)). There were 41 males (57.7%) and the mean age of patients was 42.9 years ([Table 1](#)). There were nine patients (12.7%) with DM and 39 (54.9%) with hypertension. The levels of creatinine, eGFR, and urine protein-to-creatinine ratio (UPCR) at renal biopsy were 1.24 ± 0.92 mg/dL, 84 ± 43 mL/min/1.73 m², and 2.69 ± 2.89 g/g, respectively. Based on LM types, differences in clinical findings of blood pressure, eGFR, UPCR, serum albumin, or hemoglobin were not observed; glomerular crescent was found only in PGN and tubulointerstitial changes were more dominant in FSGS. C1q intensity on IF staining did not differ among the three types. The initial pathologic diagnoses were C1qN (21 cases), IgAN (21 cases), membranous nephropathy (MN; 11 cases), FSGS (seven cases), mesangial glomerulopathy (MesG; six cases), diabetic nephropathy (three cases), MCD (one case), and acute tubulointerstitial nephritis (one case). C1qN was diagnosed as the underlying disease after 2005, 20 years after it was defined. IgAN was diagnosed based on the findings of mesangial changes in LM, dominant or codominant

intensity of IgA and/or C3 on IF staining regardless of C1q intensity, and mesangial electron-dense deposits. MesG was diagnosed based on similar criteria as IgAN; however, with lesser intensity of IgA/C3 on IF staining and lesser mesangial changes. FSGS and MCD showed lower immunoglobulin and C3 intensity and higher C1q intensity on IF staining. MN showed a thickened glomerular basement membrane with subepithelial electron-dense deposits. There were no differences in clinical and LM/EM findings between the original C1qN and the reclassified group meeting the definition of C1qN, as demonstrated in [Table 2](#). However, differences were observed in the intensity of IgA and C3 on IF staining.

Outcome-based on the histopathology of reclassified cases that met the definition of C1q nephropathy

ESRD-free survival was observed in the reclassified cases according to the type of light microscopic findings, as depicted in [Fig. 2](#). During the follow-up period, there was one case of mortality in FSGS, four cases of ESRD in PGN, two cases of ESRD in MCD, and one case of ESRD in FSGS ($p = 0.24$ by log-rank test) ([Fig. 2](#)). The risk factors for incidence of ESRD were UPCR at renal biopsy, severity of the glomerular crescent, and the amount of mesangial matrix; C1qN type was not included ([Supplementary Table 2](#), available online).

Reclassification into a group that met the definition of C1q nephropathy and the glomerulopathy not in this group

The characteristics of GN included in this group, GN without C1q stain, and GN with C1q stain on IF that did not fulfill the criteria of C1qN were compared ([Table 3](#)). FSGS, IgAN, and MN were identified because these GNs had enough patients for comparative study. Hypertension at renal biopsy was less frequent in FSGS and MN reclassified into this group than in FSGS and MN not included in this group. In patients with MN reclassified into this group, proteinuria was lower and they had more severe findings of mesangial cellular proliferation and an increased mesangial matrix than those with MN not included in this group. When comparing the characteristics between cases that fulfilled the definition of C1qN and the corre-

Table 1. Characteristics of cases reclassified by the C1q nephropathy definition according to the type classified by light microscopic examination at renal biopsy

Characteristic	Total	LM types			p-value
		FSGS	PGN	MCD	
No. of patients	71	25	20	26	
Age (yr)	42.9 ± 18.9	46.5 ± 16.1	43.1 ± 18.8	39.2 ± 21.3	0.22
Male sex	41 (57.7)	12 (48.0)	11 (55.0)	18 (69.2)	0.30
Diabetes mellitus	9 (12.7)	3 (12.0)	1 (5.0)	5 (19.2)	0.35
Hypertension	39 (54.9)	15 (60.0)	12 (60.0)	12 (46.2)	0.53
SBP (mmHg)	128 ± 23	128 ± 18	130 ± 24	127 ± 26	0.90
DBP (mmHg)	76 ± 13	76 ± 12	77 ± 14	76 ± 14	0.91
Albumin (g/dL)	3.4 ± 0.9	3.5 ± 0.8	3.2 ± 1.0	3.5 ± 1.0	0.53
Hemoglobin (g/dL)	13.4 ± 2.3	13.0 ± 1.9	13.0 ± 2.6	14.1 ± 2.3	0.07
Creatinine (mg/dL)	1.24 ± 0.92	1.39 ± 0.99	1.19 ± 0.58	1.15 ± 1.08	0.47
eGFR (mL/min/1.73 m ²)	84 ± 43	71 ± 33	89 ± 60	92 ± 34	0.13
UPCR (g/g creatinine)	2.68 ± 2.89	1.83 ± 1.96	3.71 ± 2.98	2.66 ± 3.35	0.08
Renal pathology					
LM findings					
Glomeruli					
No. of glomeruli	22.8 ± 16.5	23.8 ± 17.1	19.1 ± 12.3	24.7 ± 18.7	0.53
Global sclerosis (%)	17.9 ± 22.7	24.1 ± 22.7	16.2 ± 19.6	13.2 ± 24.3	0.046
Segmental sclerosis (%)	4.8 ± 7.9	13.6 ± 7.5	0.0 ± 0.0	0.0 ± 0.0	<0.001
Crescent (%)	0.6 ± 3.9	0.0 ± 0.0	2.2 ± 7.2	0.0 ± 0.0	0.02
Presence of ischemic change (%)	0.1 ± 0.8	0.0 ± 0.0	0.34 ± 1.50	0.0 ± 0.0	0.28
Presence of mesangial hypercellularity	9 (12.7)	2 (8.0)	7 (35.0)	0 (0)	0.001
Presence of mesangial matrix expansion	6 (8.5)	0 (0)	4 (20.0)	2 (7.7)	0.06
Tubulointerstitium					
Presence of tubulointerstitial atrophy	20 (28.2)	12 (48.0)	4 (20.0)	4 (15.4)	0.02
Presence of interstitial fibrosis	21 (28.6)	12 (48.0)	6 (30.0)	3 (11.5)	0.02
Presence of interstitial inflammation	16 (22.5)	11 (44.0)	4 (20.0)	1 (3.8)	0.003
Vessel					
Presence of arteriosclerosis	13 (18.3)	7 (28.0)	3 (15.0)	3 (11.5)	0.29
Presence of intimal thickening	20 (28.2)	8 (32.0)	5 (25.0)	7 (26.9)	0.86
IF findings					
IgG	0.90 ± 1.05	0.42 ± 0.47	0.90 ± 0.91	1.37 ± 1.33	0.03
IgM	0.93 ± 0.85	1.08 ± 0.90	1.05 ± 0.86	0.69 ± 0.78	0.19
IgA	0.90 ± 1.00	0.74 ± 1.00	1.25 ± 1.06	0.79 ± 0.93	0.19
C3	1.26 ± 1.13	0.90 ± 1.00	1.35 ± 1.09	1.54 ± 1.22	0.14
C1q	2.34 ± 0.56	2.20 ± 0.41	2.30 ± 0.47	2.50 ± 0.71	0.27
Fibrinogen	0.27 ± 0.62	0.24 ± 0.60	0.43 ± 0.82	0.17 ± 0.45	0.48
Kappa chain	0.51 ± 0.79	0.56 ± 0.63	0.30 ± 0.57	0.62 ± 1.02	0.29
Lambda chain	0.74 ± 0.96	0.96 ± 1.09	0.45 ± 0.74	0.75 ± 0.95	0.25
EM findings					
Electron-dense deposit					
Presence on mesangium	71 (100)	25 (100)	20 (100)	26 (100)	UC
Presence on subepithelial space	13 (18.3)	2 (8.0)	4 (20.0)	7 (26.9)	0.21
Presence on subendothelial space	14 (19.7)	5 (20.0)	6 (30.0)	3 (11.5)	0.30
Podocyte effacement	32 (45.1)	12 (48.0)	11 (55.0)	8 (30.8)	0.36

Data are expressed as number only, mean ± standard deviation, or number (%).

DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EM, electron microscopic examination; FSGS, focal segmental glomerulosclerosis; IF, immunofluorescent microscopic examination; Ig, immunoglobulin; LM, light microscopic examination; LM types, C1q nephropathy subgrouped by light microscopic examination; MCD, minimal change disease; PGN, proliferative glomerulonephritis; SBP, systolic blood pressure; UC, uncheckable; UPCR, urine protein-to-creatinine ratio.

Presence of pathologic findings: defined as a severity of mild or greater. The p-value was calculated by the Kruskal-Wallis test.

Table 2. Differences between patients previously diagnosed with C1qN and the group reclassified according to the definition of C1qN

Pathologic diagnosis	Original C1qN (n = 21)	Reclassified C1qN (n = 50)	p-value
Age (yr)	43.7 ± 17.9	42.5 ± 19.4	0.80
Male sex	14 (66.7)	27 (54.0)	0.32
Diabetes mellitus	2 (9.5)	7 (14.0)	0.61
Hypertension	13 (61.9)	26 (52.0)	0.44
SBP (mmHg)	127 ± 14	129 ± 26	0.69
DBP (mmHg)	75 ± 10	77 ± 14	0.52
Albumin (g/dL)	3.5 ± 1.0	3.4 ± 0.9	0.72
Hemoglobin (g/dL)	13.5 ± 2.6	13.3 ± 2.2	0.76
Creatinine (mg/dL)	1.30 ± 0.93	1.22 ± 0.93	0.84
eGFR (mL/min/1.73 m ²)	87.1 ± 54.3	82.8 ± 37.7	0.89
UPCR (g/g creatinine)	2.89 ± 3.12	2.59 ± 2.81	0.62
Renal pathology			
LM findings			
Glomeruli			
No. of glomeruli	19.1 ± 10.4	24.4 ± 18.3	0.50
Global sclerosis (%)	18.7 ± 22.9	17.5 ± 22.9	0.68
Segmental sclerosis (%)	6.3 ± 6.9	4.2 ± 8.2	0.10
Crescent (%)	0.0 ± 0.0	0.9 ± 4.6	0.26
Presence of ischemic change	0 (0)	1 (2.0)	>0.99
Presence of mesangial hypercellularity	1 (4.8)	8 (16.0)	0.26
Presence of mesangial matrix expansion	0 (0)	6 (12.0)	0.17
Tubulointerstitium			
Presence of tubulointerstitial atrophy	9 (42.9)	11 (22.0)	0.08
Presence of interstitial fibrosis	9 (42.9)	12 (24.0)	0.11
Presence of interstitial inflammation	9 (42.9)	7 (14.0)	0.008
Vessel			
Presence of arteriosclerosis	5 (23.8)	8 (16.0)	0.44
Presence of intimal thickening	7 (33.3)	13 (26.0)	0.53
IF findings			
IgG	0.60 ± 0.72	1.03 ± 1.14	0.24
IgM	0.88 ± 0.93	0.95 ± 0.82	0.56
IgA	0.26 ± 0.41	1.17 ± 1.07	0.001
C3	0.36 ± 0.45	1.64 ± 1.11	<0.001
C1q	2.24 ± 0.54	2.38 ± 0.57	0.24
Fibrinogen	0.07 ± 0.24	0.35 ± 0.71	0.10
Kappa chain	0.36 ± 0.57	0.57 ± 0.86	0.4
Lambda chain	0.41 ± 0.66	0.88 ± 1.03	0.07
EM findings			
Electron-dense deposit			
Presence on mesangium	21 (100)	50 (100)	UC
Presence on subepithelial space	1 (4.8)	12 (24.0)	0.09
Presence on subendothelial space	5 (23.8)	9 (18.0)	0.57
Podocyte effacement	13 (61.9)	19 (38.0)	0.07

Data are expressed as mean ± standard deviation or number (%).

C1qN, C1q nephropathy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EM, electron microscopic examination; Ig, immunoglobulin; IF, immunofluorescent microscopic examination; LM, light microscopic examination; SBP, systolic blood pressure; UC, uncheckable; UPCR, urine protein-to-creatinine ratio.

Presence of pathologic findings: defined as severity of mild or more. The p-value was calculated by the Mann-Whitney U test.

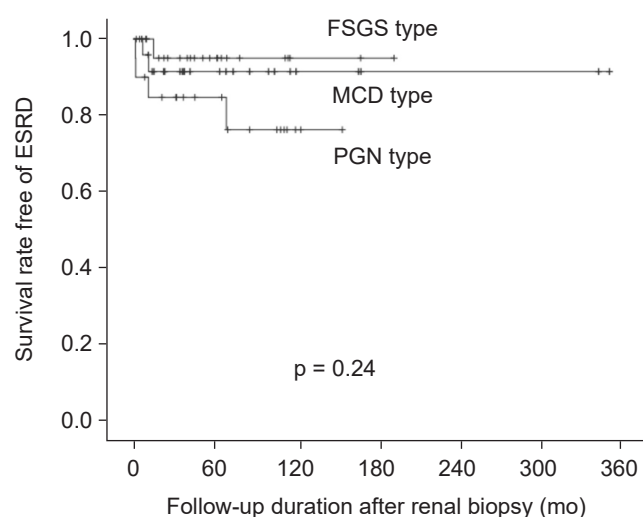


Figure 2. ESRD-free survival rate according to the type of light microscopic findings.

ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; PGN, proliferative glomerulonephritis.

sponding GNs after 1:3 matching by age and sex, as shown in Table 4, the only significant clinicopathologic finding was decreased proteinuria in patients with membranous nephropathy reclassified into this group (Table 4). Immunoglobulins showed higher intensity on IF staining of this group than GN not included in this group. Additionally, the intensity of C3 was higher in IgAN and MN reclassified into this group. Mesangial electron-dense deposits were present in all this group; however, there were differences in the frequency of mesangial electron-dense deposits in GN not included in this group. According to C1q deposition, we compared the renal survival of cases matching the definition of C1qN, GN with C1q deposition, and GN without C1q deposition. The incidence of ESRD was lower in IgAN reclassified into this group than in IgAN without C1q staining (Fig. 3). However, there were no differences in the incidence of ESRD and mortality for 1:3 matching by age and sex between GN reclassified into this group and GN without C1q staining (Supplementary Fig. 1, available online).

Discussion

This study reclassified the pathological diagnosis of kidney biopsy using the diagnostic criteria for C1qN and com-

pared the characteristics and prognosis of cases reclassified to meet the definition of C1qN with those of cases showing minimal or no C1q deposits in GNs. The only significant difference observed was decreased proteinuria in MN cases reclassified into the new group meeting the definition of C1qN compared to MN cases without C1q staining. There was no difference in renal prognosis between the GN based on the intensity of C1q staining. No differences in clinical findings and renal prognosis were observed in patients with C1qN based on LM types.

Seventy-seven patients were diagnosed with C1qN after reclassification; however, six with associated secondary diseases were excluded from this study. Complement in transthyretin amyloidosis (ATTR) is related to clinical manifestation [24]. C1q may modulate the age of onset of ATTR [25]; however, its exact role has not yet been elucidated. Amyloid fibrils interact with the complement to activate the pathway for promoting phagocytosis and lysis of opsonized fibrils [26,27]. To eliminate amyloid deposits, C1q deposits increase in the glomerulus [28–30], this may be misdiagnosed as C1qN. Systemic involvement such as Henoch-Schönlein purpura (HSP) can be excluded even if C1q is deposited in the kidney. HSP, which shows a systemic disease, appears mainly in children due to their immature immune systems, and IgAN is limited to kidneys in adults with mature immune systems [31]. Differentiation of C1qN from IgAN is necessary because of similar mesangial changes in both diseases. Complement activation via the alternative or lectin pathway is crucial in the pathogenesis of IgAN [10,32], and the role of C1q activation via the classical pathway is largely unknown [9]. Our study showed that the degree of IgA and C3 deposits was significantly higher in reclassified C1qN, especially in 20 patients of IgAN, than in the initially diagnosed C1qN. When C1q, IgA, and C3 appear at high intensity simultaneously, other diagnostic markers such as the serum IgA/C3 ratio are needed to differentiate both diseases.

The relationship between C1q activation and the pathogenesis of GNs associated with alternative and/or lectin pathway activation is unclear because C1q detection in renal tissues is not an essential diagnostic marker. Renal outcomes based on the presence of C1q deposits in several GNs have been reported [13–21]. The clinicopathologic features and prognosis of IgAN based on C1q deposits varied in each study [13,14,16,17]. Patients with IgAN with renal

Table 3. Differences in characteristics between cases reclassified according to the definition of C1qN and corresponding glomerulopathy cases

Pathologic diagnosis	FSGS without C1q (n = 1,492)	FSGS with C1q (n = 196)	FSGS reclassified to C1qN (n = 7)	IgAN without C1q (n = 6,789)	IgAN with C1q (n = 761)	IgAN reclassified to C1qN (n = 21)	MN without C1q (n = 1,574)	MN with C1q (n = 448)	MN reclassified to C1qN (n = 11)
Age (yr)	45.3 ± 18.1	43.9 ± 17.7	41.1 ± 12.7	37.7 ± 15.0	41.0 ± 15.1	40.4 ± 21.5*	52.6 ± 15.0	54.4 ± 14.8	56.5 ± 17.1
Male sex	874 (58.6)	102 (52.0)	3 (42.9)	3,523 (51.9)	376 (49.4)	14 (66.7)	953 (60.5)	282 (62.9)	5 (45.5)
Diabetes mellitus	203 (13.6)	32 (16.3)	1 (14.3)	436 (6.4)	73 (9.6)	1 (4.8)*	219 (13.9)	79 (17.6)	2 (18.2)
Hypertension	942 (63.1)	149 (76.0)	2 (28.6)*	3,153 (46.4)	463 (60.8)	12 (57.1)*	884 (56.2)	291 (65.0)	6 (54.5)*
SBP (mmHg)	129 ± 18	131 ± 17	121 ± 15	125 ± 18	127 ± 18	126 ± 26*	127 ± 18	128 ± 18	134 ± 33
DBP (mmHg)	80 ± 13	81 ± 12	76 ± 9	78 ± 13	77 ± 13	74 ± 15	79 ± 13	78 ± 13	82 ± 15
Albumin (g/dL)	3.3 ± 1.0	3.4 ± 1.0	3.2 ± 1.0	3.9 ± 0.7	3.8 ± 0.7	3.5 ± 0.9*	2.7 ± 0.8	2.7 ± 0.8	3.2 ± 1.0
Hemoglobin (g/dL)	13.0 ± 2.4	13.0 ± 2.2	12.7 ± 1.4	13.0 ± 2.0	12.8 ± 2.1	13.7 ± 2.1	13.1 ± 2.0	13.0 ± 1.9	14.3 ± 1.7
Creatinine (mg/dL)	1.63 ± 1.48	1.46 ± 1.16	1.46 ± 1.10	1.29 ± 1.27	1.39 ± 1.44	1.12 ± 0.47	1.05 ± 0.73	1.06 ± 1.04	0.90 ± 0.22
eGFR (mL/min/1.73 m ²)	67.1 ± 37.7	72.8 ± 42.0	67.5 ± 31.4	82.0 ± 80.7	79.9 ± 46.8	84.0 ± 35.6	90.0 ± 38.5	95.3 ± 42.9	84.3 ± 20.5*
UPCR (g/g creatinine)	4.09 ± 4.72	4.66 ± 4.80	2.54 ± 3.22	1.78 ± 2.47	2.27 ± 2.96	1.73 ± 1.73*	5.74 ± 4.54	5.13 ± 4.37	3.31 ± 2.74*
Renal pathology									
LM findings									
Glomeruli									
No. of glomeruli	21.3 ± 18.8	17.8 ± 14.1	14.0 ± 8.5	23.0 ± 20.0	19.6 ± 13.2	24.9 ± 17.9	22.0 ± 20.7	20.6 ± 15.0	35.0 ± 24.6
Global sclerosis (%)	23.2 ± 22.6	23.0 ± 23.0	23.3 ± 26.6	17.4 ± 20.8	20.9 ± 22.8	20.1 ± 22.2*	9.9 ± 15.0	10.2 ± 15.4	6.3 ± 9.1
Segmental sclerosis (%)	11.8 ± 14.1	14.5 ± 14.0	15.9 ± 11.7*	7.3 ± 12.0	7.6 ± 11.8	4.3 ± 7.6	2.2 ± 7.1	3.12 ± 8.54	0.5 ± 1.8
Crescent (%)	0.9 ± 6.6	0.3 ± 1.9	0.0 ± 0.0	2.3 ± 7.5	3.3 ± 10.3	0.6 ± 2.2	0.5 ± 4.5	0.32 ± 2.52	0.0 ± 0.0
Presence of ischemic change	62 (4.2)	11 (5.6)	0 (0)	164 (2.4)	10 (1.3)	1 (4.8)	39 (2.5)	7 (1.6)	0 (0)
Presence of mesangial hypercellularity	45 (3.0)	2 (1.0)	0 (0)	1,296 (19.7)	158 (20.8)	4 (19.1)	20 (1.3)	8 (1.8)	2 (18.2)*
Presence of mesangial matrix expansion	29 (1.9)	3 (1.5)	0 (0)	905 (13.3)	126 (16.6)	1 (4.8)*	25 (1.6)	4 (0.9)	2 (18.2)*
Tubulointerstitium									
Presence of tubulointerstitial fibrosis	544 (36.5)	71 (36.2)	1 (14.3)	1,721 (25.3)	216 (28.4)	3 (14.3)	229 (14.5)	62 (13.8)	3 (27.3)
Presence of interstitial fibrosis	552 (37.8)	68 (34.7)	1 (14.3)	1,635 (24.1)	197 (25.9)	5 (23.8)	224 (14.2)	58 (12.9)	3 (27.3)
Presence of interstitial inflammation	425 (28.5)	52 (26.5)	1 (14.3)	1,426 (21.0)	179 (23.5)	3 (14.3)	166 (10.5)	51 (11.4)	2 (18.2)
Vessel									
Presence of arteriosclerosis	297 (19.9)	35 (17.9)	0 (0)	804 (11.8)	104 (13.7)	3 (14.3)	163 (10.4)	44 (9.8)	2 (18.2)
Presence of intimal thickening	403 (27.0)	66 (33.7)	2 (28.6)	1,271 (18.7)	178 (23.4)	5 (23.8)*	270 (17.2)	107 (23.9)	4 (36.4)*
IF findings									
IgG	0.06 ± 0.23	0.17 ± 0.43	0.07 ± 0.19*	0.21 ± 0.48	0.52 ± 0.67	0.67 ± 1.00*	1.15 ± 1.23	2.53 ± 0.85	2.18 ± 1.09*
IgM	0.22 ± 0.48	0.97 ± 0.78	0.93 ± 0.84*	0.41 ± 0.60	0.95 ± 0.64	0.93 ± 0.74*	0.17 ± 0.43	0.56 ± 0.60	0.86 ± 0.95*
IgA	0.10 ± 0.34	0.32 ± 0.58	0.14 ± 0.38*	1.44 ± 1.23	1.39 ± 0.81	1.93 ± 0.78*	0.21 ± 0.55	0.80 ± 0.86	0.86 ± 1.14*
C3	0.23 ± 0.54	0.76 ± 0.91	0.29 ± 0.39*	0.87 ± 0.98	1.75 ± 0.91	1.95 ± 0.97*	0.52 ± 0.75	1.50 ± 0.90	2.09 ± 0.54*
C1q	0.00 ± 0.00	0.94 ± 0.59	2.00 ± 0.00*	0.00 ± 0.00	0.78 ± 0.41	2.38 ± 0.59*	0.00 ± 0.00	1.05 ± 0.59	2.91 ± 1.14*
Fibrinogen	0.05 ± 0.24	0.31 ± 0.63	0.14 ± 0.38*	0.25 ± 0.59	0.63 ± 0.84	0.57 ± 0.93*	0.09 ± 0.31	0.42 ± 0.64	0.23 ± 0.61
Kappa chain	0.04 ± 0.21	0.20 ± 0.51	0.21 ± 0.39*	0.29 ± 0.67	0.63 ± 0.87	0.48 ± 0.60*	0.40 ± 0.90	1.37 ± 1.29	1.09 ± 1.30*
Lambda chain	0.05 ± 0.22	0.29 ± 0.61	0.50 ± 0.76*	0.46 ± 0.91	1.07 ± 1.17	1.07 ± 1.04*	0.39 ± 0.88	1.31 ± 1.26	1.09 ± 1.22*

(Continued to the next page)

Table 3. Continued

Pathologic diagnosis	FSGS without C1q (n = 1,492)	FSGS with C1q (n = 196)	FSGS reclassified to C1qN (n = 7)	IgAN without C1q (n = 6,789)	IgAN with C1q (n = 761)	IgAN reclassified to C1qN (n = 21)	MN without C1q (n = 1,574)	MN with C1q (n = 448)	MN reclassified to C1qN (n = 11)
EM findings									
Electron-dense deposit									
Presence on mesangium	187 (12.5)	28 (14.3)	7 (100)*	5,384 (79.3)	641 (84.2)	21 (100)*	218 (13.9)	104 (23.2)	11 (100)*
Presence on subepithelial space	24 (1.6)	6 (3.1)	0 (0)	239 (3.5)	48 (6.3)	1 (4.8)*	1,192 (75.7)	399 (89.1)	10 (90.9)*
Presence on subendothelial space	71 (4.8)	21 (10.7)	0 (0)*	573 (8.4)	106 (13.9)	4 (19.0)*	94 (6.0)	39 (8.7)	3 (27.3)*
Podocyte effacement	635 (42.6)	94 (48.0)	2 (28.6)	1,150 (16.9)	181 (23.8)	5 (23.8)*	867 (55.1)	337 (75.2)	9 (81.8)*

Data are expressed as mean ± standard deviation or number (%). C1qN, C1q nephropathy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EM, electron microscopic examination; FSGS, focal segmental glomerulosclerosis; IF, immunofluorescent microscopic examination; Ig, immunoglobulin; IgAN, IgA nephropathy; LM, light microscopic examination; MN, membranous nephropathy; SBP, systolic blood pressure; UPCR, urine protein-to-creatinine ratio.

Presence of pathologic findings: defined as a severity of mild or greater. The p-value was calculated by the Kruskal-Wallis test.

*p < 0.05.

C1q deposits had higher grades of endocapillary hypercellularity, tubular atrophy or interstitial fibrosis, cellular crescent, IgG, IgM, and C4 deposits than those with IgAN without C1q deposits [17]. Additionally, these patients did not achieve clinical remission and progressed to ESRD [13,17]. Conversely, other studies reported no significant association between C1q deposits and clinical features of patients with IgAN [16]. C1q deposits in MN are suggestive of secondary MN, such as SLE; however, it appears in some cases of primary MN [18], though C1q activation does not mediate renal damage [18]. A study comparing the pathological findings and clinical prognosis of FSGS and C1qN reported no significant differences in LM findings of renal pathology, except for the degree of FSGS; hence, C1q positivity was not associated with poor renal prognosis [15].

Our study showed that renal pathologies, conforming to the C1qN criteria, were categorized at initial assessment into other diseases, such as IgAN, MN, FSGS, and MesG. There are several clinicopathologic characteristics between GN reclassified into the new group meeting the definition of C1qN and GN without C1q staining on IF before matching. However, the only significant finding was decreased proteinuria in patients with MN reclassified into this group meeting the definition of C1qN after 1:3 matching by age and sex. It is unclear whether C1q deposits result from classical pathway activation in MN, IgAN, and FSGS, or if they have a specific process to be redefined as another pathologic diagnosis of C1qN. In this study, the analysis did not reveal any significant differences in pathologic findings, renal function, and outcome between GN without C1q deposits and reclassified cases that met the definition of C1qN. Therefore, the role of C1q deposits in GN is unclear. However, C1q deposits were associated with poor renal outcomes, and its pathophysiologic role in the prognosis of GN can be speculated as the co-deposition of IgG, IgM, and C1q that constitute a membrane attack complex [17]. This induces renal inflammation and fibrosis, leading to endothelial cell proliferation and cellular crescent formation, resulting in poor renal outcomes [17]. However, there is insufficient evidence that C1q deposition is a pathophysiologic process causing other GN diseases, or that high intensity of C1q deposition can have different clinicopathologic characteristics and renal outcomes within GN. Therefore, additional research is needed on whether to redefine the subtype from existing GN or define it as C1qN.

Table 4. Characteristics among cases that met the definition of C1qN and the corresponding glomerulopathy without C1q staining

Pathologic diagnosis	FSGS (n = 21)	FSGS reclassified to C1qN (n = 7)	IgAN (n = 63)	IgAN reclassified to C1qN (n = 21)	MN (n = 33)	MN reclassified to C1qN (n = 11)
Age (yr)	41.0 ± 12.1	41.1 ± 12.7	40.4 ± 21.3	40.4 ± 21.5	56.6 ± 16.6	56.5 ± 17.1
Male sex	9 (42.9)	3 (42.9)	42 (66.7)	14 (66.7)	15 (45.5)	5 (45.5)
Diabetes mellitus	2 (9.5)	1 (14.3)	6 (9.5)	1 (4.8)	6 (18.2)	2 (18.2)
Hypertension	13 (61.9)	2 (28.6)	32 (50.8)	12 (57.1)	23 (69.7)	6 (54.5)
SBP (mmHg)	131 ± 15	121 ± 15	126 ± 18	126 ± 26	132 ± 15	134 ± 33
DBP (mmHg)	82 ± 14	76 ± 9	77 ± 12	74 ± 15	81 ± 13	82 ± 15
Albumin (g/dL)	3.1 ± 1.0	3.2 ± 1.0	3.7 ± 0.7	3.5 ± 0.9	2.8 ± 0.7	3.2 ± 1.0
Hemoglobin (g/dL)	13.4 ± 1.9	12.7 ± 1.4	12.9 ± 1.8	13.7 ± 2.1	13.2 ± 1.9	14.3 ± 1.7
Creatinine (mg/dL)	1.35 ± 1.08	1.46 ± 1.10	1.20 ± 0.91	1.12 ± 0.47	1.08 ± 0.65	0.90 ± 0.22
eGFR (mL/min/1.73 m ²)	83.2 ± 61.8	67.5 ± 31.4	82.3 ± 31.2	84.0 ± 35.6	81.1 ± 32.1	84.3 ± 20.5
UPCR (g/g creatinine)	4.48 ± 5.02	2.54 ± 3.22	3.08 ± 4.5	1.73 ± 1.73	6.01 ± 4.25	3.31 ± 2.74*
Renal pathology						
LM findings						
Glomeruli						
No. of glomeruli	30.0 ± 22.9	14.0 ± 8.5	17.3 ± 17.0	24.9 ± 17.9*	23.6 ± 14.3	35.0 ± 24.6
Global sclerosis (%)	17.4 ± 20.5	23.3 ± 26.6	15.8 ± 19.3	20.1 ± 22.2	13.3 ± 17.8	6.3 ± 9.1
Segmental sclerosis (%)	10.8 ± 10.7	15.9 ± 11.7	5.7 ± 10.1	4.3 ± 7.6	0.9 ± 2.9	0.5 ± 1.8
Crescent (%)	0.3 ± 0.9	0.0 ± 0.0	3.3 ± 7.2	0.6 ± 2.2	0.1 ± 0.8	0.0 ± 0.0
Presence of ischemic change	3 (14.3)	0 (0)	2 (3.2)	1 (4.8)	1 (3.0)	0 (0)
Presence of mesangial hypercellularity	2 (9.5)	0 (0)	14 (22.2)	4 (19.0)	1 (3.0)	2 (18.2)
Presence of mesangial matrix expansion	1 (4.8)	0 (0)	12 (19.0)	1 (4.8)	1 (3.0)	2 (18.2)
Tubulointerstitium						
Presence of tubulatrophy	7 (33.3)	1 (14.3)	12 (19.0)	3 (14.3)	7 (21.2)	3 (27.3)
Presence of interstitial fibrosis	7 (33.3)	1 (14.3)	13 (20.6)	5 (23.8)	3 (9.1)	3 (27.3)
Presence of interstitial inflammation	4 (19.0)	1 (14.3)	10 (15.9)	3 (14.3)	5 (15.2)	2 (18.2)
Vessel						
Presence of arteriosclerosis	2 (9.5)	0 (0)	7 (11.1)	3 (14.3)	4 (12.1)	2 (18.2)
Presence of intimal thickening	7 (33.3)	2 (28.6)	13 (20.6)	5 (23.8)	9 (27.3)	4 (36.4)
IF findings						
IgG	0.14 ± 0.36	0.07 ± 0.19	0.21 ± 0.49	0.67 ± 1.00*	1.03 ± 1.20	2.18 ± 1.09*
IgM	0.07 ± 0.24	0.93 ± 0.84*	0.48 ± 0.68	0.93 ± 0.74	0.20 ± 0.47	0.86 ± 0.95*
IgA	0.10 ± 0.44	0.14 ± 0.38	1.52 ± 1.31	1.93 ± 0.78*	0.32 ± 0.92	0.86 ± 1.14
C3	0.12 ± 0.44	0.29 ± 0.39	0.88 ± 0.96	1.95 ± 0.97*	0.70 ± 1.07	2.09 ± 0.54*
C1q	0.00 ± 0.00	2.00 ± 0.00*	0.00 ± 0.00	2.38 ± 0.59*	0.00 ± 0.00	2.91 ± 1.14*
Fibrinogen	0.02 ± 0.11	0.14 ± 0.38	0.21 ± 0.54	0.57 ± 0.93	0.02 ± 0.09	0.23 ± 0.61
Kappa chain	0.05 ± 0.22	0.21 ± 0.39	0.38 ± 0.77	0.48 ± 0.60	0.44 ± 0.97	1.09 ± 1.30
Lambda chain	0.12 ± 0.44	0.50 ± 0.76	0.48 ± 0.94	1.07 ± 1.04*	0.39 ± 0.89	1.09 ± 1.22
EM findings						
Electron-dense deposit						
Presence on mesangium	5 (23.8)	7 (100)*	47 (74.6)	21 (100)*	7 (21.2)	11 (100)*
Presence on subepithelial space	0 (0)	0 (0)	2 (3.2)	1 (4.8)	27 (81.8)	10 (90.9)
Presence on subendothelial space	1 (4.8)	0 (0)	3 (4.8)	4 (19.0)	2 (6.1)	3 (27.3)
Podocyte effacement	10 (47.6)	2 (28.6)	11 (17.5)	5 (23.8)	20 (60.6)	9 (81.8)

Data are expressed as mean ± standard deviation or number (%).

C1qN, C1q nephropathy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration; FSGS, focal segmental glomerulosclerosis; EM, electron microscopic examination; IF, immunofluorescent microscopic examination; Ig, immunoglobulin; IgAN, IgA nephropathy; LM, light microscopic examination; MN, membranous nephropathy; SBP, systolic blood pressure; UPCR, urine protein-to-creatinine ratio.

Presence of pathologic findings: defined as severity of mild or more. The p-value was calculated by the Mann-Whitney U test.

*p < 0.05.

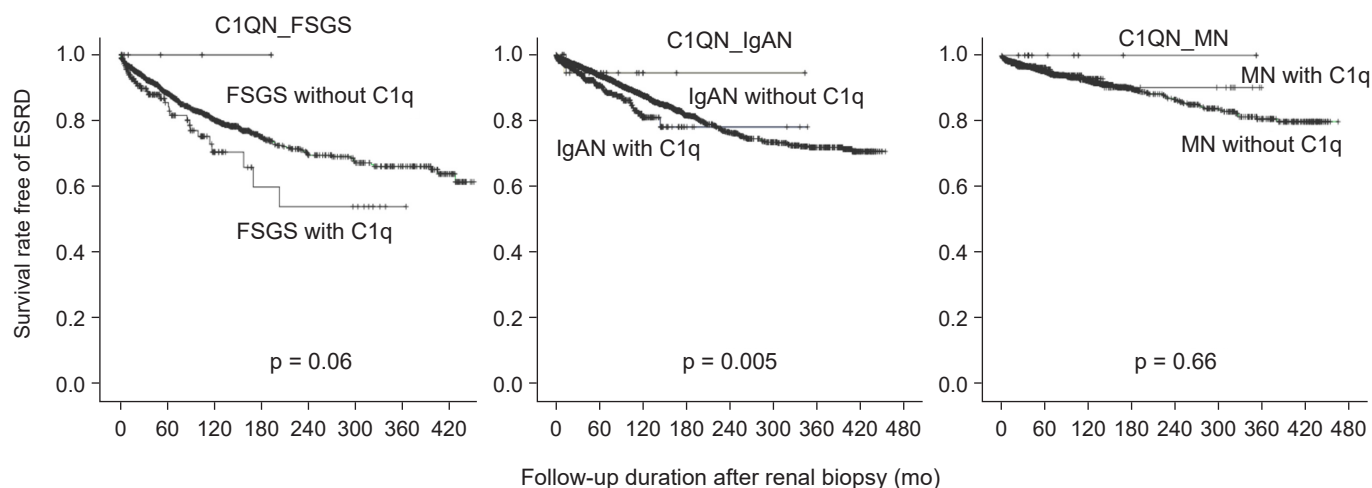


Figure 3. Renal survival according to the amount of C1q deposition in FSGS, IgAN, and MN.

C1qN, C1q nephropathy; C1qN_FSGS, after reclassification from FSGS to cases meeting the definition of C1qN; C1qN_IgAN, after reclassification from IgAN to cases meeting the definition of C1qN; C1qN_MN, after reclassification from MN to cases meeting the definition of C1qN; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; MN, membranous nephropathy.

Our study has some limitations. First, other confounding factors may exist despite conducting the data analysis by matching by age and sex to minimize the bias between patients with and without C1q deposits. Second, our study included only Koreans; thus, generalizing the results to other populations is not feasible. The prevalence of GN depends on racial factors and C1q deposits may vary [13,14,16,33–36], requiring a different diagnostic approach to C1qN. Third, the determination of prospective interventions and treatments that affect the prognosis of patients with C1q deposits is difficult because our study is based on retrospective data extracted from the renal biopsy registry. In addition, there is a risk that immunofluorescence, which is critical for the diagnosis of C1qN, may not have been evaluated consistently by the same person, as retrospective data from each hospital were collected and reclassified based on the results.

However, to the best of our knowledge, our study is the first to compare the clinicopathological significance of C1q deposits between cases meeting the definition GN reclassified into C1qN and GNs with minimal or without C1q staining after matching by age and sex. Additionally, it is possible to hypothesize the results of classical pathway activation in GN other than C1qN by comparing the presence or absence of C1q deposits in various GNs, rather than in one.

In conclusion, C1q deposits in GN were predicted to lead to more aggressive renal inflammation and fibrosis than in conventional GN; however, this was not confirmed in our study. Furthermore, the reclassification cases meeting the definition of C1qN using predefined criteria did not suggest any other clinicopathological indications to define a new disease process. These findings suggest that the classical pathway activation in some GN has no apparent direct effect on renal impairment, and may not have a pathogenic role in GN development and progression. Hence, further studies on this topic are needed.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization: HJC

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