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Are serum C3 levels or kidney C3 deposits useful markers for predicting outcomes in patients with ANCA-associated vasculitis?

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ABSTRACT

Introduction: Complement activation emerged as a key actor of anti-neutrophil cytoplasmic antibodies-associated vasculitis (AAV). Whether serum levels of C3 (sC3) or C3 kidney deposition may help to refine the prognosis of AAV remains elusive.

Methods: Retrospective multicentric study that included 154 patients with a first flare of AAV and sC3 (n = 143) or C3 kidney staining (n = 95) available at diagnosis. Clinical presentations, kidney pathology, and survival of patients with normal or low sC3 were compared using univariate analyses, Kaplan-Maier curves with log-rank comparison, or multivariate Cox' model, as appropriate.

Results: 20 patients (14 %) had low sC3. sC3 (as bivariate low/normal or as a continuous variable) was associated with 5-year mortality but not with kidney survival. C3 kidney deposition (C3+) was identified in 23 patients who were characterized by more frequent chronic hypertension and lower eGFR at presentation ($p = 0.04$). C3+ correlated with IgG, IgM, C1q deposition ($p = 0.07$, $p < 0.0001$ and $p = 0.003$, respectively). Chronicity and activity scores were similar in C3+ and C3- patients. Among C3+ patients, those with C3 deposition ≥2+ had lower eGFR at presentation ($p = 0.006$) and were more frequently classified as sclerotic using the Berden classification ($p = 0.04$) and as 'high risk' using the Brix score ($p = 0.03$). However, eGFR improvement following induction regimen was similar between C3+ and C3- patients, and kidney survival at 5 years was similar.

Conclusions: Correlation of sC3 with mortality confirms mechanistic links between complement pathways and AAV, but the lack of clear predictive sC3 cut-off and the similar kidney outcome irrespective of C3 deposition precludes their use as biomarkers of AAV outcomes and response to treatment.

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1. Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a severe form of systemic pauci-immune vasculitis. High serum levels of cleaved complement factors Bb, C3a and C5a during AAV flares suggest that alternative complement pathway activation promotes or modulates AAV in humans [1]. This was demonstrated in animal models of pauci-immune glomerulonephritis induced by anti-myeloperoxidase (MPO) antibodies transfer and led to the identification of C5a receptor (C5a-R1/CD88) as a key player in AAV that can be targeted in humans [2].

C3 is pivotal in the complement pathway system given its position upstream of the terminal C5b9 membrane attack complex and downstream of the various complement activation pathways (classical, alternative, and lectins pathways). C3 and C5 cleavage products C3a and C5a are potent anaphylatoxins attracting and activating inflammatory cells such as neutrophils and monocytes. Systemic activation of the alternative complement pathway (soluble part) can be partly estimated by measuring the serum level of C3, whereas local tissue activation (contact part) can be estimated with the staining of C3 cleavage products C3c or C3d on biopsies.

Recently, an association between serum C3 levels at the onset of AAV flare with mortality and/or kidney outcome was reported [3–7], suggesting that serum C3 levels (sC3) or C3 immunostaining may be easy-to-use biomarkers of AAV prognosis and help to develop personalized complement-directed treatment. These findings must be used with caution, given the lack of clear sC3 cut-off correlating with mortality risk, the normality of serum C3 levels in most AAV patients and the uncoupling between serum C3 levels and C3 deposition within injured tissue, including the kidney [8].

In this multicenter retrospective cohort study that included 154 AAV patients, we assessed the potential relationship between serum C3 levels (sC3) or glomerular C3 deposition and the outcome of patients developing AAV.

2. Materials and methods

In this multicentric retrospective study, we included patients with AAV (granulomatosis with polyangiitis or microscopic polyangiitis) and kidney involvement who were referred between 2004 and 2019 in 8 departments of Nephrology or Internal Medicine in France or in Luxembourg. Patients with eosinophilic granulomatosis with polyangiitis were excluded from the analysis.

2.1. Definitions and clinical data

AAV was defined according to the 1990 American College of Rheumatology classification criteria and/or revised Chapel Hill consensus conference nomenclature of vasculitides [9,10]. Activity of the AAV was assessed using the Birmingham Vasculitis Activity Score (BVAS) [11]. Glomerular filtration rate was estimated using the CKD-EPI formula. Clinical data included demographic profile and routine clinical and laboratory findings that were obtained from medical records. Serum C3 was measured using nephelemetry COBA 8000 (normal range 0.8–1.51 g/L). In addition to high dose corticosteroids, patients received one of three induction therapy strategies used in daily practice during the study period: (1) rituximab administration of 4 weekly infusions of 375 mg/m^2 or 1 g, 2 weeks apart; (2) cyclophosphamide infusion of 0.6 g/m^2 on days 1, 15, and 29, then 0.7 g/m^2 every 21 days; or (3) rituximab administration of 4 weekly infusions of 375 mg/m^2 plus cyclophosphamide infusion of 500 mg on days 1 and 15.

2.2. Kidney biopsies

Processing of kidney biopsies included light microscopy and immunofluorescence (IF). For light microscopy, all cases were stained with hematoxylin and eosin, periodic acid-Schiff, Masson's trichrome and Jones methenamine silver. For IF, 0.3 μm cryostat sections were stained with polyclonal antibodies to IgG, IgM, IgA, C3, C1q, kappa, lambda and fibrinogen (rabbit, polyclonal, Agilent).

2.3. Statistics

Continuous variables are expressed as means and standard deviation and compared with the Mann-Whitney test. Discontinuous variables are expressed as numbers and percentages and compared with the Fisher's exact test. Survival curves were plotted according to the Kaplan-Meier method and comparisons between groups were performed using the Log Rank test (univariate analysis). The following variables were entered in various multivariable Cox models: age, ANCA type, serum creatinine at diagnosis, sC3, immunosuppressive regimen, BVAS. To be considered significant, the p-value had to be lower than 0.05. Statistical analyses were performed using the Xlstat and GraphPad (Prism9) software.

2.4. Ethics

This study was conducted according to the Helsinki declaration, as revised in 2004, was approved by the Institutional Review Board of the University Hospital of Toulouse (agreement number RnIPH 2023–37) According to its recommendations, written informed consent was waived.

3. Results

3.1. Serum C3 levels and survival

Among the 154 patients with new-onset AAV included in the study (anti-MPO antibodies n = 90, anti-PR3 antibodies n = 48, double positivity anti-MPO and anti-PR3 n = 1, no ANCA n = 4), sC3 at the onset of flare was available in 143. Low sC3 (<0.8 g/L) was identified in 20 patients. Characteristics of this cohort are summarized in Table 1 (overall cohort and for each sub-groups defined according to the serum C3 level: <1 g/L, 1–1.5 g/L and >1.5 g/L).

As shown in Fig. 1, five-year survival was significantly lower in patients with low sC3 at diagnosis, compared to those with normal sC3. Five patients died during the first year of follow-up: cause of death was a cardiac arrest in 3 and sepsis in 2. After adjustment on age, serum creatinine at presentation, induction regimen, BVAS or ANCA subtypes, sC3 as a continuous variable or as binary variable (low vs. normal sC3) remained associated with mortality (Table 2). However, sC3 was not associated with dialysis-free survival (Fig. 1) nor with incidence of infection. Of note, serum C3 and C4 levels were significantly correlated ($r^2 = 0.2$; $p < 0.0001$).

3.2. C3 deposits and kidney presentation

Among the 95 patients with a kidney biopsy at AAV flare and C3 immunostaining available (but no circulating anti-GBM antibodies), 66 patients had anti-MPO antibodies, 28 had anti-PR3 antibodies and 1 individual had both anti-MPO and anti-PR3 antibodies (Table 3).

Glomerular C3 deposition (≥1+) was identified in 23 patients and correlated with IgM and C1q deposits ($p < 0.0001$ and $p = 0.003$, respectively), but intensity of glomerular and tubular C3 deposits did not correlate. Glomerular IgG deposits were more frequently seen in patients with C3 deposition, but this did not reach statistical significance ($p = 0.07$). Incidence of focal and segmental glomerulosclerosis was similar in C3 positive and negative patients, as well as the percentage of sclerotic or crescentic glomeruli, and the percentage of glomeruli with rupture of Bowman's capsule. Brix and Nezam scores were similar in both groups. Of note, patients with C3 deposition on kidney biopsy more frequently had a history of hypertension and lower eGFR at presentation

Table 1
Clinical characteristics of 143 patients with AAV and serum levels of C3 available at diagnosis. Patients were divided in 3 groups according to their serum C3 level (first quartile, second & third quartiles, fourth quartile). *BVAS*, Birmingham vasculitis activity score; *eGFR*, estimated glomerular filtration rate; *MPO*, myeloperoxidase; *PR3*, Proteinase-3; *SD,* standard deviation. * One patient had both anti-MPO and anti-PR3 antibodies. Four patients had no ANCA.

Clinical Characteristics	Serum C3				
	Overall Cohort N = 143	<1 g/L N = 38	1–1.5 g/L N = 71	>1.5 g/L N = 34	*P*-value
Male gender (n, %)	78 (57)	20 (57)	43 (61)	15 (47)	0.41
Age (years; mean ± SD)	67 ± 13	70 ± 13	68 ± 12	62 ± 14	0.03
Diabetes mellitus (n, %)	15 (10)	6 (16)	6 (8)	3 (9)	0.54
Hypertension (n, %)	63 (44)	19 (50)	34 (48)	10 (29)	0.15
Baseline eGFR (mL/min/1.7m2, mean ± SD)	65 ± 26	61 ± 26	65 ± 27	69 ± 25	0.61
Vasculitis at flare					
Anti-MPO antibodies (n, %) *	90 (64)	24 (67)	50 (70)	16 (47)	0.06
Anti-PR3 antibodies (n, %)	48 (34)	11 (29)	20 (28)	17 (50)	0.08
Concomitant anti-GBM antibodies (n, %)	55	18 (47)	25 (35)	12 (35)	0.42
BVAS (mean ± SD)	18 ± 7	18 ± 8	18 ± 7	20 ± 6	0.25
eGFR (mL/min/1.7m2, mean ± SD)	28 ± 27	20 ± 24	29 ± 27	35 ± 28	0.004
Urinary protein to creatinine ratio (g/g; mean ± SD)	2.2 ± 3.3	2.1 ± 1.9	2.4 ± 4.3	2.1 ± 2.3	0.90
Serum levels of C4 (g/L; mL/min/1.7m2; mean ± SD)	0.28 ± 0.11	0.22 ± 0.11	0.29 ± 0.08	0.33 ± 0.12	<0.0001
Immunosuppressive regimen (induction; n, %)					0.59
Cyclophosphamide	77	23 (61)	34 (48)	20 (59)	
Rituximab	47	10 (26)	28 (39)	9 (26)	
Cyclophosphamide + Rituximab	19	5 (13)	9 (13)	5 (15)	

(19 ± 18 vs. 29 ± 25 mL/min/1.73 m^2, p = 0.04), while other clinical characteristics before the AAV flare and at presentation were similar.

Lastly, compared to patients with no or low C3 deposition (0–1+), patients with C3 deposition ≥2+ had lower eGFR at presentation (10 ± 7 vs. 28 ± 24 mL/min/1.73 m^2, p = 0.006), were more frequently classified as sclerotic using the Berden classification (p = 0.04) and as 'high risk' using the Brix score (p = 0.03), and had a higher Nezam score (p = 0.04). Other clinical characteristics were not different between the two groups.

3.3. Glomerular C3 deposits and kidney outcome

As shown in Fig. 1, eGFR improvement following induction regimen was similar between patients with and without C3 deposition. Dialysis-free survival at 5 years was also similar, even after adjustment on age, immunosuppressive regimen, and Berden classification or Brix score.

4. Discussion

In this retrospective multicentric study, we aimed to assess the potential use of sC3 and glomerular C3 deposition as predictive biomarkers of overall and kidney survivals in AAV patients. The main relationship between sC3 and survival was observed during the first weeks of follow-up, but the underlying molecular mechanisms remain elusive. Despite some appealing correlations suggesting C3 be a potential biomarker, several pitfalls preclude its use as a single biomarker of AAV activity or prognosis. In recent studies, sC3 was associated with overall prognosis but the cut-off used was within normal values and varied among studies [3,4,6,7,12] precluding its use as a robust predictive biomarker. In addition, according to our findings, correlation between sC3 at diagnosis and kidney survival was not reproducible.

In our series, sC3 correlated with sC4, suggesting a more complex interaction of the alternative and classical complement pathways in AAV. The various levels of systemic inflammation in AAV patients may also have altered sC3 independently of the complement activation. Before using sC3 as a simple biomarker of mortality risk in AAV patients, further studies are thus needed. Among others, these studies should ideally report the serum level of both C3 and C3 fragments (especially the anaphylatoxin C3a) to characterize C3 activation at diagnosis, but also during remission periods to decipher how such assessment may help to furnish information on AAV activity and risk of kidney failure. They should also integrate the closed correlation between complement activation and age and gender that was demonstrated in healthy individuals [13]. Lastly, the relationship between sC3 and cardiovascular risk also prompts further refinement of the interplay between AAV, sC3, systemic inflammation, and conventional cardiovascular risks in patients with chronic kidney disease [14].

In the present study, C3 deposition within the kidney was associated with lower eGFR at presentation but only C3 deposition ≥2+ was associated with significantly different histological lesions (i.e., more chronic lesions). Moreover, the concomitant deposition of C3 with IgM, IgG or C1q in most biopsies also points to mechanisms of complement activation not only related to the alternative pathway activation by the AAV *per se*, but also to immunoglobulin-dependent activation, as already noticed [5,6]. Even though a study by Hakroush et al. recently reported an intrarenal synthesis of C3 during AAV-RPGN that may correlate with kidney presentation and outcome [8], our findings obtained in a larger cohort indirectly suggest that C3 consumption and deposition in glomeruli may derive from both classical and alternative pathway activation. If confirmed, these results suggest that targeting alternative complement pathway only using dedicated complement inhibitors upstream C3 may incompletely block complement activation-induced kidney lesions in AAV.

This study has several limitations, mainly related to its retrospective design. Immunosuppressive regimens were not standardized, but previous studies demonstrated the similar outcome of AAV patients receiving rituximab or cyclophosphamide as induction regimen [15]. Also, high dose of methylprednisolone and induction regimen had no impact upon renal and overall prognosis. Soluble markers of alternative complement pathway activation (serum levels of factor B, factor H, C3a, C5a, and C5b9) were not available, but the aim of this study was to study the potential of sC3, a dosing regularly performed during the diagnosis work-up of RPGN and vasculitis, and C3 immunostaining as simple predictive biomarkers of AAV outcome. Last, C3 production by tubular cells could not be accurately assessed.

5. Conclusions

Despite the confirmation of a dose-dependent correlation between sC3 and 5-year survival in AAV patients and the lower eGFR at presentation in patients with C3 deposition within glomeruli, the lack of clear predictive sC3 cut-off and the similar kidney outcome irrespective of C3 deposits precludes the use of C3 as a biomarker of AAV overall or kidney outcomes. Whether products of C3 cleavage like C3a, or combinations of C3a, C5a and soluble C5b9 may help to identify patients who are more prone to respond to anti-complement therapy remains to be determined.

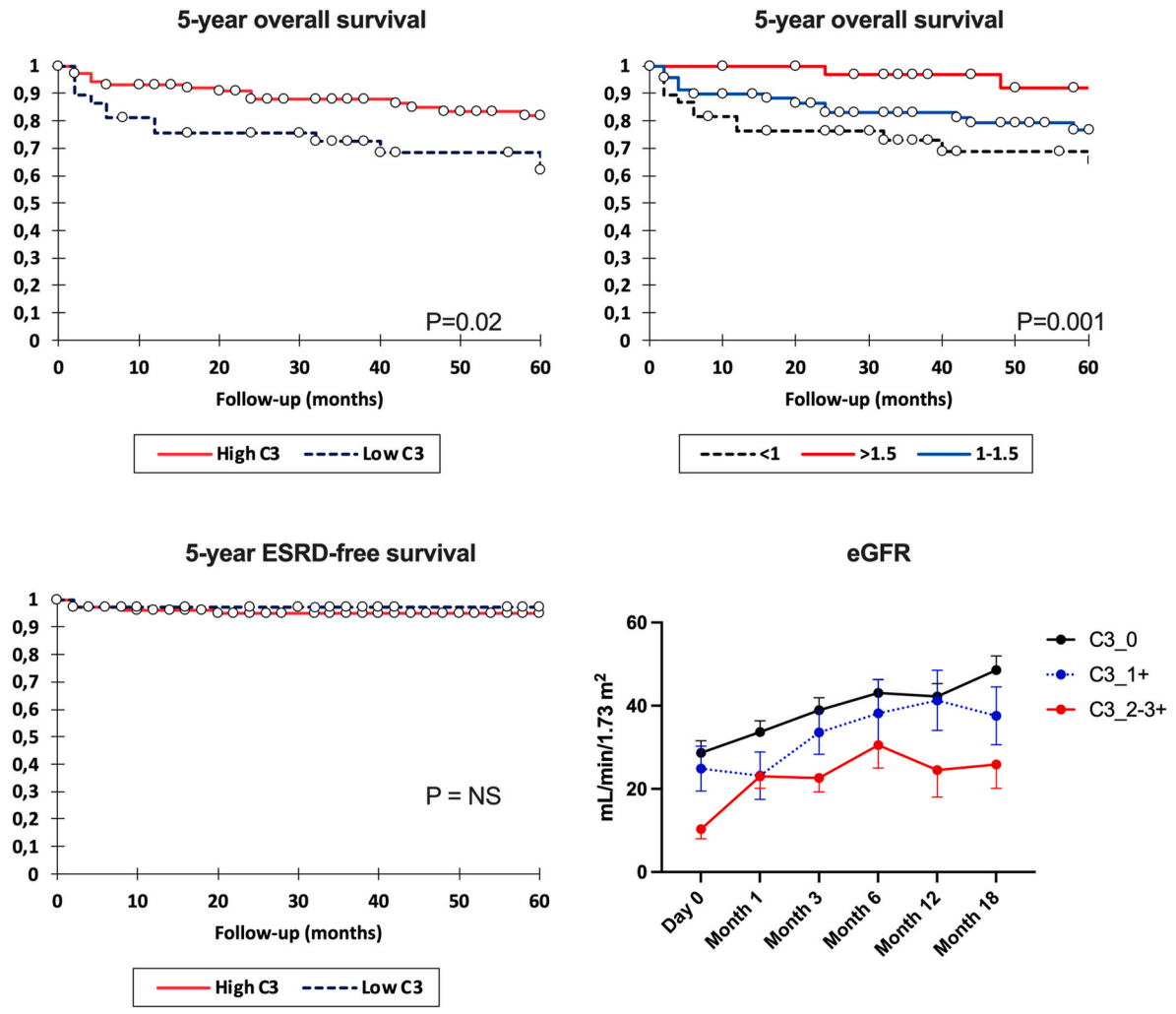

Fig. 1. A-C. Overall (**A - B**) and end-stage renal disease-free (**C**) survival curves of 143 patients with ANCA-associated vasculitis according to their soluble C3 at diagnosis (low: C3<0.8 g/L). **D.** Estimated glomerular filtration rate of 95 patients with ANCA-associated vasculitis according to the deposition or not of C3 within glomeruli.

Table 2
Serum C3 at diagnosis is independently associated with overall survival in patients with ANCA-associated vasculitis (multivariate analysis using Cox model). *RTX*, rituximab; *CYC*, cyclophosphamide.

Variable	Odd-ratio	95 % Confidence intervalle	p-value
Age (years)	1.071	1.025–1.120	0.002
Serum creatinine at diagnosis (μmol/L)	0.999	0.997–1.001	0.315
Serum C3 (g/L)	0.174	0.000–0.616	0.007
Induction with RTX (vs. CYC)	0.702	0.288–1.710	0.436
Induction with RTX + CYC (vs. CYC)	1.188	0.339–4.158	0.788

Credit author statement

Alexis CASSARD Conceptualization; Data curation; Formal analysis, Writing – review & editing; Clément KOUNDE Conceptualization; Data curation; Formal analysis, Writing – review & editing; Laurence BOUILLET Data curation, Writing – review & editing; Tiphaine GOULENOK Data curation, Writing – review & editing; David RIBES Conceptualization, Data curation, Writing – review & editing; Rafik MESBAH Data curation, Writing – review & editing; Vincent LANGLOIS Data curation, Writing – review & editing; Audrey DELAS Formal analysis; Writing – review & editing; Françoise FORTENFANT Formal analysis; Writing – review & editing; Sébastien HUMBERT Data curation, Writing – review & editing; Céline LEBAS Data curation, Writing – review & editing; Julie BELLIERE Data curation, Writing – review & editing; Philippe KERSCHEN Data curation, Writing – review & editing; Dominique CHAUVEAU Conceptualization; Writing – review & editing; Magali COLOMBAT Formal analysis; Writing – review & editing; Stanislas FAGUER Conceptualization; Data curation, Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing; Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Declaration of competing interest

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Table 3
Clinical characteristics of 95 patients with AAV and kidney biopsy available at diagnosis (but no circulating anti-GBM antibodies). *BVAS*, Birmingham vasculitis activity score; *eGFR*, estimated glomerular filtration rate; *MPO*, myeloperoxidase; *PR3*, proteinase-3; *SD,* standard deviation. * One patient had both anti-PR3 and anti-MPO antibodies. Two patients had no circulating ANCA.

Clinical Characteristics		C3 deposits		
	Overall Cohort N = 95	No N = 72	≥1+ N = 23	*P*-value
Male gender (n, %)	56 (59)	45 (62)	11 (48)	0.23
Age (years; mean ± SD)	66 ± 14	66 ± 12	66 ± 17	0.72
Diabetes mellitus (n, %)	8 (8.5)	6 (8)	2 (8)	1.00
Hypertension (n, %)	37 (39)	33 (46)	4 (17)	0.02
Baseline eGFR (mL/min/1.7m2, mean ± SD)	73 ± 23	72.3 ± 24	75 ± 21	0.72
Vasculitis at flare				
Anti-MPO antibodies (n, %)	66 (69)	51 (71)	15 (65)	0.60
Anti-PR3 antibodies (n, %)*	28 (30)	20 (28)	8 (35)	0.60
BVAS at flare (mean ± SD)	18 ± 6	18 ± 7	18 ± 5	0.93
eGFR (mL/min/1.7m2, mean ± SD)	26 ± 23	29 ± 24	19 ± 18	0.04
Urinary protein to creatinine ratio (g/g; mean ± SD)	2 ± 2.5	1.9 ± 2.5	2.3 ± 2.5	0.27
Serum levels of C3 (g/L; mL/min/1.7m2; mean ± SD)	1.23 ± 0.4	1.28 ± 0.4	1.1 ± 0.4	0.07
Serum levels of C4 (g/L; mL/min/1.7m2; mean ± SD)	0.27 ± 0.1	0.28 ± 0.1	0.24 ± 0.1	0.28
Kidney biopsy				
Percentage of sclerosed glomeruli (n, %)	25 ± 22	24 ± 21	30 ± 25	0.33
Percentage of crescentic glomeruli (n, %)	32 ± 24	31 ± 23	36 ± 25	0.38
Bowman capsule rupture (n, %)	34 (36)	29 (40)	5 (22)	0.14
Focal and segmental glomerulosclerosis (n, %)	12 (13)	9 (12)	3 (13)	1.00
Brix score (n, %) (*n = 90)				0.10
Low risk	31 (34)	27 (40)	4 (17)	
Medium risk	34 (38)	24 (36)	10 (44)	
High	25 (28)	16 (24)	9 (39)	
Berden score (n, %)				0.40
Focal	29 (30.5)	25 (35)	4 (17)	
Crescentic	21 (22)	15 (21)	6 (26)	
Mixed	33 (35)	24 (33)	9 (39)	
Sclerotic	12 (13)	8 (11)	4 (17)	
Nezam score	1.38 ± 9.8	1.14 ± 9.3	2.13 ± 11.5	0.71
Arteriolar vasculitis (n, %)	15 (16)	13 (18)	2 (8)	0.35
Immune deposits (n, %)				
Glomeruli				
IgG ≥1+	19 (20)	11 (15)	8 (35)	0.07
IgA ≥1+	7 (7)	4 (6)	3 (13)	0.35
IgM ≥1+	16 (17)	5 (7)	11 (48)	<0.0001
C1q ≥ 1+	6 (7)	1 (1)	5 (22)	0.003
C3 ≥1+	23 (24)	–	–	–
≥2+	9 (9)	–	–	–
Peri-tubular				
C3 ≥1+	7	4 (5)	3 (13)	0.34

conflict of interests.

Data availability

Data will be made available on request.

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NA.

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