

Glomerular C4d Deposition and Kidney Disease Progression in IgA Nephropathy: A Systematic Review and Meta-analysis

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Background: Glomerular deposition of C4d is a widely used biomarker for activation of the lectin pathway in the complement system and is reported to be associated with kidney progression in immunoglobulin A nephropathy (IgAN). The aim of this study was to evaluate whether glomerular C4d deposition, as a new biomarker, improves the prediction of kidney prognosis in IgAN.

Study Design: Systematic review and meta-analysis.

Setting & Population: Patients with biopsy-proven primary IgAN without age limitations.

Selection Criteria for Studies: Cross-sectional or cohort studies reporting the prevalence of glomerular C4d deposition or evaluating its association with IgAN progression.

Predictor: Glomerular C4d deposition.

Outcome: Composite progression event of a >30% decline in estimated glomerular filtration rate or end-stage kidney disease.

Results: 12 studies with 1,251 patients were included. The prevalence of glomerular C4d deposition was 34% (95% CI, 27%-41%), with large heterogeneity ($I^2 = 86%$; $P < 0.001$). Patients with C4d deposition had lower estimated glomerular filtration

rates (mean difference [MD], -11.48 ; 95% CI, -18.27 to -4.70 ; $P < 0.001$) as well as higher urinary protein-creatinine ratios (MD, 0.87 ; 95% CI, 0.53 - 1.21 ; $P < 0.001$) or 24-hour urinary protein excretion (MD, 0.99 ; 95% CI, 0.50 - 1.47 ; $P < 0.001$) and higher risk for hypertension (relative risk [RR], 1.45 ; 95% CI, 1.06 - 1.99 ; $P = 0.02$) than patients without C4d deposition. Glomerular C4d deposition was associated with a high Oxford classification score, including M1, E1, S1, and T1/2 lesions (all $P \leq 0.006$). Patients with C4d deposition had higher rates of use of renin-angiotensin system blockers and immunosuppressants. Glomerular C4d was found to be a risk factor for the composite kidney event (RR, 3.17 ; 95% CI, 2.29 - 4.40 ; $P < 0.001$; adjusted HR, 2.05 ; 95% CI, 1.53 - 2.76 ; $P < 0.001$) and end-stage kidney disease (RR, 4.37 ; 95% CI, 3.15 - 6.07 ; $P < 0.001$) without evidence of heterogeneity.

Limitations: The definition of positive C4d was not uniform and not all studies provided data about kidney outcomes.

Conclusions: Glomerular C4d deposition is associated with an adverse prognosis and may be a useful biomarker of disease prediction in IgAN.

Complete author and article information provided before references.

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Immunoglobulin A (IgA) nephropathy (IgAN) is the most common primary glomerular disease worldwide and features dominant deposition of IgA1 and C3 in the mesangium.^{1,2} The clinical manifestation and prognosis of IgAN vary, ranging from mild hematuria and proteinuria to kidney failure.² Approximately 20% to 40% of cases will progress to end-stage kidney disease (ESKD) within 10 to 20 years.^{3,4} Therefore, investigating indicators for disease progression and early identification of ESKD in high-risk individuals is of great importance.

Recent studies suggest that the complement cascade is involved in the pathogenesis and progression of IgAN.^{5,6} Several studies have proved that lectin pathway activation is associated with serious clinical and pathologic presentations and poor long-term renal survival in both children and adults.⁷⁻¹⁶ C4d is the cleavage product of C4, which covalently binds to the cell surface through thioester bonds,^{17,18} and a common downstream marker of the lectin and classical pathways. Because the classical pathway is not involved in the pathogenesis of IgAN, C4d deposition is thought to be associated with activation of the lectin

pathway. It is speculated that C4d deposition might be an indicator for predicting the severity of IgAN and a risk factor for kidney outcomes. However, the prevalence of glomerular C4d deposits has been inconsistent in different studies or populations. Most studies have small sample sizes or end point events, which limits the study power.

Therefore, in this systematic review and meta-analysis, we aimed to investigate the prevalence of glomerular C4d deposits in IgAN, as well as the predictive value of C4d for kidney outcomes in different ethnic populations, stages of kidney disease, or levels of proteinuria.

METHODS

Search Strategy

We searched for articles in the PubMed and EMBASE databases indexed before March 29, 2020, without language restrictions. We combined the subject words and free words to obtain all related articles, for example, “IGA nephropathy” and “complement component 4d” (a detailed search strategy is provided in Table S1). All

PLAIN-LANGUAGE SUMMARY

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease worldwide. The clinical manifestation and prognosis of IgAN vary greatly, ranging from mild hematuria and proteinuria to kidney failure. Therefore, investigating indicators for disease progression and early identification of end-stage kidney disease in high-risk individuals is of great importance. We searched PubMed and EMBASE databases for articles about C4d deposition in IgAN and the prognostic value of C4d in IgAN. Glomerular C4d deposits were associated with severe clinical and pathologic characteristics. C4d deposition was an independent risk factor for kidney failure in IgAN even in normal kidney function. These results support the hypothesis that glomerular C4d is a potentially useful biomarker for predicting prognosis in IgAN.

documents were imported into Endnote X9 to remove duplicate documents. Two authors (Y.J. and J.Z.) read the article title, abstract, and full text in sequence according to inclusion and exclusion criteria and filtered the articles that met inclusion criteria. The inclusion criteria and analysis were specified in advance and documented in a protocol. The study's registration number is CRD42020185862 (registered on PROSPERO).

Inclusion and Exclusion Criteria

We included cross-sectional or cohort studies reporting the prevalence of glomerular C4d deposition and evaluated its association with IgAN progression. We excluded studies that only measured C4d in urine or serum. The exclusion criteria also included nonoriginal research, case reports, studies of secondary IgAN, and lack of comparison between groups.

Study Quality Assessment and Data Extraction

The Newcastle-Ottawa quality assessment scale was used to evaluate the quality of cohort studies, and the Agency for Healthcare Research and Quality (AHRQ) checklist was applied for cross-sectional studies. The results of the AHRQ checklist and Newcastle-Ottawa scale for relevant studies are shown in Tables S2 and S3, respectively. The following data were extracted: author, year, country, type of study, definition of C4d positivity, baseline age, sex, number of patients with hypertension and macroscopic hematuria, proteinuria, serum creatinine level, estimated glomerular filtration rate (eGFR), Oxford classification, use of angiotensin-converting enzyme inhibition or angiotensin receptor blocker medication, immunosuppression, and follow-up time in years. The primary outcome was a composite of a >30% decline in eGFR from the baseline value, or the onset of ESKD during the follow-up period. For dichotomous variables, number of events and total

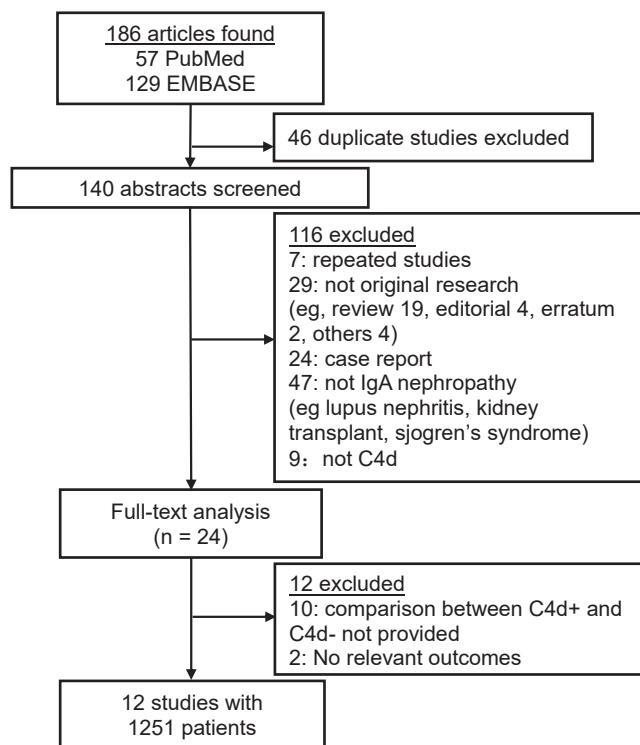


Figure 1. Flow chart for study selection. Abbreviation: IgA, immunoglobulin A.

sample size were collected. For continuous variables, mean and standard deviation or median and quartile were collected. Hypertension in children was defined as more than the 95th percentile value of the group with same age, sex, and height and in adults was defined as blood pressure $\geq 140/90$ mm Hg at the time of kidney biopsy. Mean eGFR and mean albuminuria at the time of kidney biopsy were used for subgroup analysis.

To ensure accuracy, the literature search and selection, data extraction, and quality assessment of all eligible literature were carried out independently by 2 authors (Y.J. and J.Z.). A third reviewer (J.L.) resolved any discrepancies regarding the eligibility or quality of a study.

Statistical Analysis

The relative risk (RR) and corresponding 95% CI were used to measure the effect of dichotomous variables. In several studies, continuous variables with a non-normal distribution were summarized as the median and lower quartile-upper quartile. In these cases, we used the method proposed by Hozo et al¹⁹ to estimate the mean and standard deviation. The weighted mean difference (MD) was used to compare group differences. We applied a random-effects model to synthesize the data from primary studies. Heterogeneity assessment was performed using χ^2 test and I^2 test. The cutoff values for low, moderate, and high heterogeneity were 25%, 50%, and 75%, respectively. Subgroup analysis was also conducted to explore potential

Table 1. Clinical and Pathologic Characteristics of Included Cohort Studies

Study, y	Nam et al ²¹ (2020)	Sato et al ¹⁰ (2019)	Segarra et al ⁹ (2018)	Fabiano et al ¹⁶ (2017)	Sahin et al ¹³ (2014)	Espinosa et al ¹² (2014)
Country	Korea	Japan	Spain	Brazil	Turkey	Spain
No. of patients	380	25	190	47	33	283
Age, y (C4d+/C4d-)	37.2/35.8	9.5/13.0	28.0/29.0	10.5/8.8	32.2/36.3	38.6/39.4
Patients C4d+	72 (18.9%)	14 (56.0%)	38 (20.0%)	10 (21.3%)	11 (33.3%)	109 (38.5%)
Definition of C4d positivity	>25% G	>50% G	>1 G	>50% G	>75% G	>25% G
C4d staining method	IHC	IF	IHC	IHC	IHC	IHC
Male sex (C4d+/C4d-)	48.6%/41.9%	43.0%/27.0%	63.0%/65.0%	60.0%/62.0%	55.0%/50.0%	74.0%/73.0%
Follow-up, y	7.9	2.0	15.8	5.6/9.5	2.7	6.0
Proteinuria (g/d or g/g) (C4d+/C4d-)	1.6/0.7	2.0/0.8	1.9/1.5	0.9/0.1	4.0/1.3	2.2/1.7
Baseline eGFR, mL/min/1.73 m ² (C4d+/C4d-)	72.8/88.0	121.0 /125.0	98.0/99.0	127.0/148.5	45.6/68.7	58.9/73.2
Serum creatinine, mg/dL (C4d+/C4d-)	1.4/1.0	NA	1.0/1.0	NA	3.0/1.8	NA
Macroscopic hematuria (C4d+/C4d-)	NA	64.0%/45.0%	42.0%/43.0%	NA	NA	39.0%/49.0%
Hypertension (C4d+/C4d-)	41.7%/47.1%	NA	16.0%/12.0%	10.0%/22.0%	64.0%/36.0%	72.0%/44.0%
M1 (C4d+/C4d-)	39/80	12/9	15/42	3/13	11/6	77/106
E1 (C4d+/C4d-)	11/40	4/1	5/14	1/3	NA	28/34
S1 (C4d+/C4d-)	51/191	9/4	6/16	2/10	10/8	35/22
T (1) (C4d+/C4d-)	19/18	0(7/1)	12/28	1/0	7/3	41/49
T (2) (C4d+/C4d-)	1/3	0	3/14	NA	NA	53/28
C (1) (C4d+/C4d-)	13/34	10/6	NA	NA	NA	NA
C (2) (C4d+/C4d-)	2 /7	NA	NA	NA	NA	NA
RAS blockers (C4d+/C4d-)	63/201	14/10	32/123	7/14	NA	90/135
immunosuppression (C4d+/C4d-)	11/21	11/7	26/47	7/7	58/102	19/6

Abbreviations and Definitions: >1G, >1 nonsclerotic glomeruli; >25%G, >25% of nonsclerotic glomeruli; >50%G, >50% of nonsclerotic glomeruli; >75% G, >75% of nonsclerotic glomeruli; eGFR, estimated glomerular filtration rate; g/d, unit of 24-hour urinary protein excretion; g/g, unit of urinary protein-creatinine ratio; IF, immunofluorescence; IHC, immunohistochemical; macroscopic hematuria, the presence of macroscopic hematuria at the time of the biopsy or the patient had a history of macroscopic hematuria bouts; NA, not applicable; RAS, renin-angiotensin system.

sources of heterogeneity. Publication bias was assessed by inspecting a funnel plot. All statistical tests were bilateral, and $P < 0.05$ was considered significant. Statistical analyses were performed with RevMan software (version 5.3; Cochrane Collaboration).

RESULTS

Characteristics of Included Studies

A total of 12 studies^{8-14,16,20-23} with 1,251 patients were included. Reasons for exclusion are listed in Fig 1. All 12 studies in the present analysis provided clinical and pathologic data; however, the data presentations differed. Characteristics of the included studies are summarized in Tables 1 and 2. The studies involved 7 cohort and 5 cross-sectional studies. Nine studies^{9-14,16,21,22} described the definition of glomerular C4d deposition, but the definition was inconsistent: “C4d positive” was defined as C4d deposition in >25% of nonsclerotic glomeruli in 3 studies,^{12,14,21} >50% in 4 studies,^{10,11,16,22} >75% in 1 study,¹³ or greater than any 1 of nonsclerotic glomeruli in another study.⁹ Four studies^{10,11,21,23} ($n = 484$) recruited patients from Asian populations, including Japanese and Korean patients, and 8 studies^{8,9,12-14,16,20,22} ($n = 767$)

mainly recruited from European and South American populations. Five of the 7 cohort studies^{12,13,16,21,22} ($n = 817$) with a mean follow-up of 5.7 years provided 199 composite kidney events and 126 ESKD events; these 5 studies were used to analyze the predictive value of C4d deposition to kidney event.

Prevalence of C4d Deposition in Patients With IgAN

A total of 12 studies with 1,251 participants reported the prevalence of glomerular C4d deposition in IgAN. Overall, the prevalence of C4d deposits was 34% (95% CI, 27%-41%; Fig 2), with high heterogeneity ($I^2 = 86%$; $P < 0.001$). Subgroup analysis was performed based on age, race, and the definition of C4d positivity and showed no heterogeneity (all $P > 0.05$). The prevalence in studies defining C4d positivity as C4d deposition in >25%,^{12,14,21} >50%,^{10,11,16,22} >75%,¹³ or any⁹ of nonsclerotic glomeruli was 33% (95% CI, 16%-49%), 40% (95% CI, 24%-56%), 33% (95% CI, 17%-49%), and 20% (95% CI, 14%-26%), respectively (Fig S1). Although the prevalence of C4d deposition showed a higher trend in the Asian population (46%; 95% CI, 21%-71%) than in the non-Asian populations (30%; 95% CI, 23%-36%), significance was not reached ($P = 0.22$; Fig 2).

Table 2. Clinical and Pathologic Characteristics of Included Cross-sectional Studies

Study, y	Baek et al ²³ (2018)	Wągrowska-Danilewicz et al ⁸ (2017)	Heybeli et al ¹⁴ (2015)	Maeng et al ¹¹ (2013)	Faria et al ²² (2015)	Roos et al ²⁰ (2006)
Country	Korea	Poland	Turkey	Korea	Portugal	Netherlands
No. of patients	56	43	37	23	74	60
Age, y (C4d+/C4d-)	11.5/12.8	37.0/33.0	45.6/36.1	NA	39.0	27.0/35.0
Patients C4d+	31 (55.4%)	11 (25.6%)	16 (43.2%)	13 (56.5%)	25 (34.0%)	15 (25.0%)
Definition of C4d positivity	NA	NA	>25% G	>50% G	>50% G	>1 G
C4d staining method	IHC	IF	IHC	IHC	IHC	IHC
Male sex (C4d+/C4d-)	65.0%/52.0%	73.0%/66.0%	75.0%/67.0%	NA	50.0%	67.0%/51.0%
Follow-up, y	3.6	NA	NA	NA	4.0	NA
Proteinuria (g/d or g/g) (C4d+/C4d-)	1.4/0.3	NA	2.9/1.1	NA	2.0	2.5/0.7
Baseline eGFR, mL/min/1.73 m ² (C4d+/C4d-)	105.9/114.0	NA	54.9/82.9	NA	67.5	NA
Serum creatinine, mg/dL (C4d+/C4d-)	0.6/0.5	NA	NA	NA	NA	1.5/1.1
Macroscopic hematuria (C4d+/C4d-)	52.0%/64.0%	NA	13.0%/43.0%	NA	27.0%	13.0%/40.0%
Hypertension (C4d+/C4d-)	6.4%/4.0%	73.0%/38.0%	69.0%/29.0%	NA	44.0%	NA
M1 (C4d+/C4d-)	21/2	9/27	15/13	NA	64	NA
E1 (C4d+/C4d-)	9/3	7/10	13/4	NA	50	NA
S1 (C4d+/C4d-)	4/1	8/24	14/13	NA	11	NA
T (1) (C4d+/C4d-)	1/0	NA	6/6	NA	35(1/2)	NA
T (2) (C4d+/C4d-)	1/0	6/5	9/1	NA	NA	NA
C (1) (C4d+/C4d-)	NA	NA	NA	NA	NA	NA
C (2) (C4d+/C4d-)	NA	NA	NA	NA	NA	NA
RAS blockers (C4d+/C4d-)	27/22	NA	NA	NA	NA	NA
Immunosuppression (C4d+/C4d-)	NA	NA	NA	NA	NA	NA

Abbreviations and Definitions: >1G, >1 nonsclerotic glomeruli; >25%G, >25% of nonsclerotic glomeruli; >50%G, >50% of nonsclerotic glomeruli; >75% G, >75% of nonsclerotic glomeruli; eGFR, estimated glomerular filtration rate; g/d, unit of 24-hour urinary protein excretion; g/g, unit of urinary protein-creatinine ratio; IF, immunofluorescence; IHC, immunohistochemical; macroscopic hematuria, the presence of macroscopic hematuria at the time of the biopsy or the patient had a history of macroscopic hematuria bouts; NA, not applicable; RAS, renin-angiotensin system.

Association Between C4d and Clinicopathologic Characteristics

Associations between C4d deposition and clinical characteristics are illustrated in Fig 3A. Compared with patients without glomerular C4d deposition, those with such deposition (8 studies with 1,051 patients) had lower eGFRs (MD, -11.48; 95% CI, -18.27 to -4.70; $P < 0.001$), with heterogeneity ($I^2 = 80\%$; $P < 0.001$).^{9,10,12-14,16,21,23} Glomerular C4d-positive patients also exhibited higher urinary protein-creatinine ratios (MD, 0.87; 95% CI, 0.53-1.21; $P < 0.001$) or 24-hour urinary protein excretion (MD, 0.99; 95% CI, 0.50-1.47; $P < 0.001$)^{9,10,12-14,16,21,23} than glomerular C4d-negative patients. Eight studies^{8,9,12-14,16,21,23} reported that C4d-positive patients had a high risk for hypertension (RR, 1.45; 95% CI, 1.06-1.99; $P = 0.02$). There was no significant difference between C4d-positive and -negative groups in regard to hematuria^{9,10,12,14,20,23} (RR, 0.83; 95% CI, 0.63-1.09; $P = 0.18$). Nine studies^{8-10,12-14,16,21,23} with 1,094 patients found associations between C4d deposition and pathologic lesions based on the Oxford

classification (Fig 3B). Patients with C4d deposition more frequently showed M1 (RR, 1.50; 95% CI, 1.12-1.99; $P = 0.006$), E1 (RR, 1.65; 95% CI, 1.23-2.22; $P < 0.001$), S1 (RR, 1.50; 95% CI, 1.12-1.99; $P = 0.006$), and T1/T2 (RR, 2.53; 95% CI, 1.81-3.53; $P < 0.001$) lesions than those without C4d deposition. Patients with C4d deposition had higher rates of use of renin-angiotensin system blockers (RR, 1.13; 95% CI, 1.00-1.28; $P = 0.05$) and immunosuppressants (RR, 1.83; 95% CI, 1.13 -2.97; $P = 0.01$) than those without C4d deposition.

C4d Deposition Associated With Disease Progression

Five studies^{14,15,18,21,22} with 817 patients described 199 composite kidney events and 126 ESKD events. In pooled analysis (5 studies with 817 participants), patients with glomerular C4d deposition showed a high risk for composite kidney events (RR, 3.17; 95% CI, 2.29-4.40; $P < 0.001$; $I^2 = 32\%$; $P = 0.21$) or ESKD (RR, 4.37; 95% CI, 3.15-6.07; $P < 0.001$; $I^2 = 0\%$; $P = 0.80$), with no heterogeneity (Fig 4). After adjusting for potential confounders (5

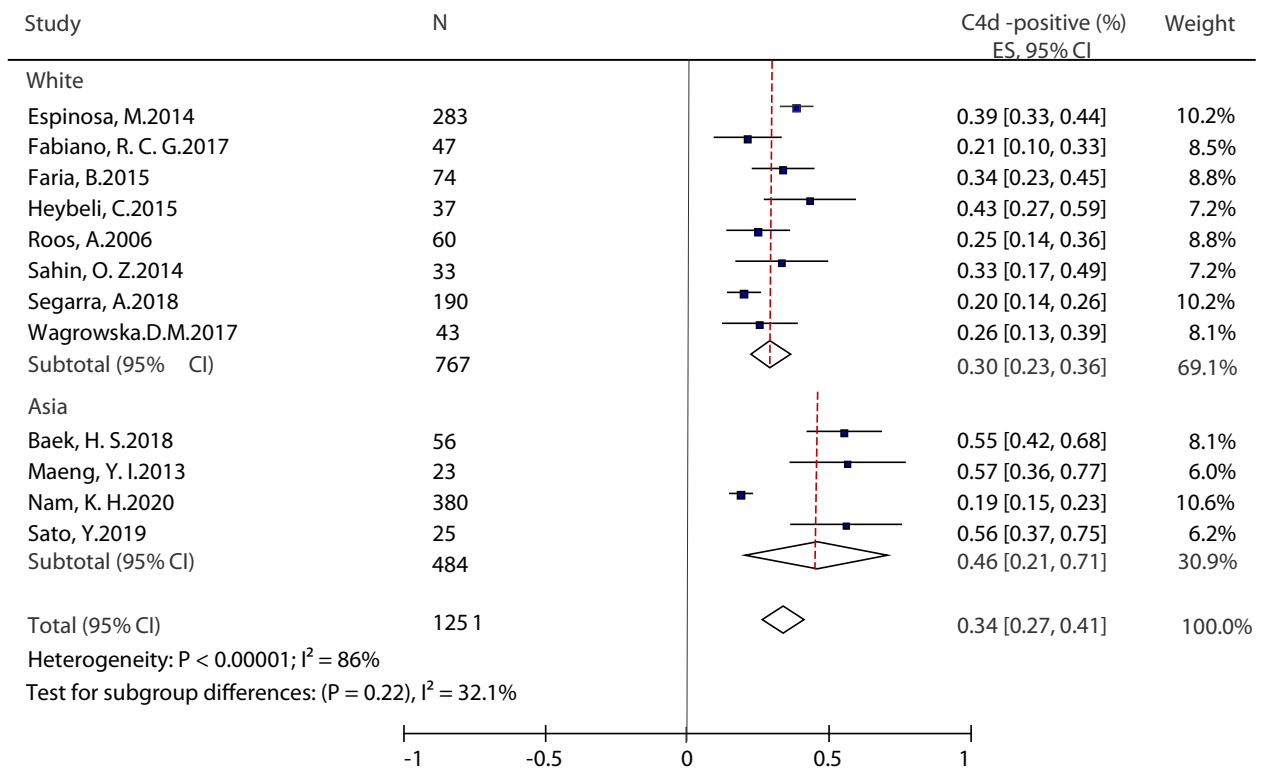


Figure 2. Forest plot for the prevalence of C4d deposition in immunoglobulin A nephropathy (subgroup analysis was performed by race).

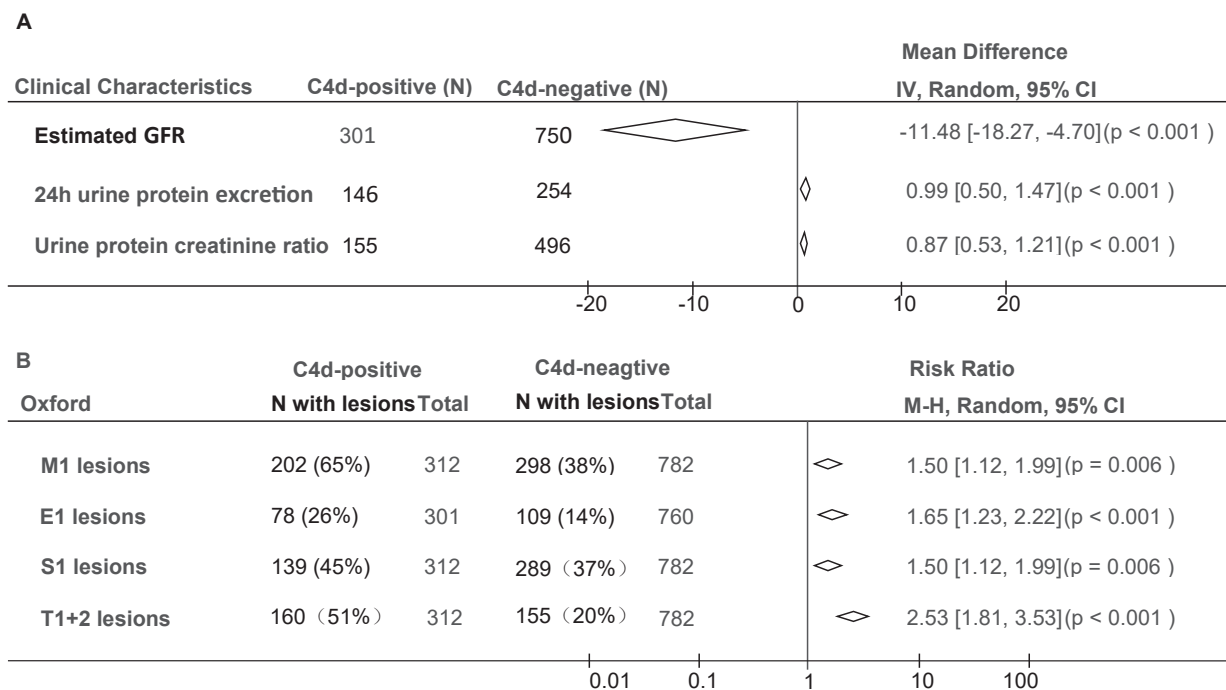


Figure 3. Forest plot for the associations between C4d deposition with the (A) clinical indicators and (B) pathologic lesions in Oxford classification. Abbreviations and Definitions: E1, any endocapillary hypercellularity lesion present; GFR, glomerular filtration rate; M1, mesangial hypercellularity score > 0.5; M-H, Mantel-Haenszel; S1, presence of segmental glomerulosclerosis; T1, >25% but <50% tubular atrophy/interstitial fibrosis; T2, >50% tubular atrophy/interstitial fibrosis.

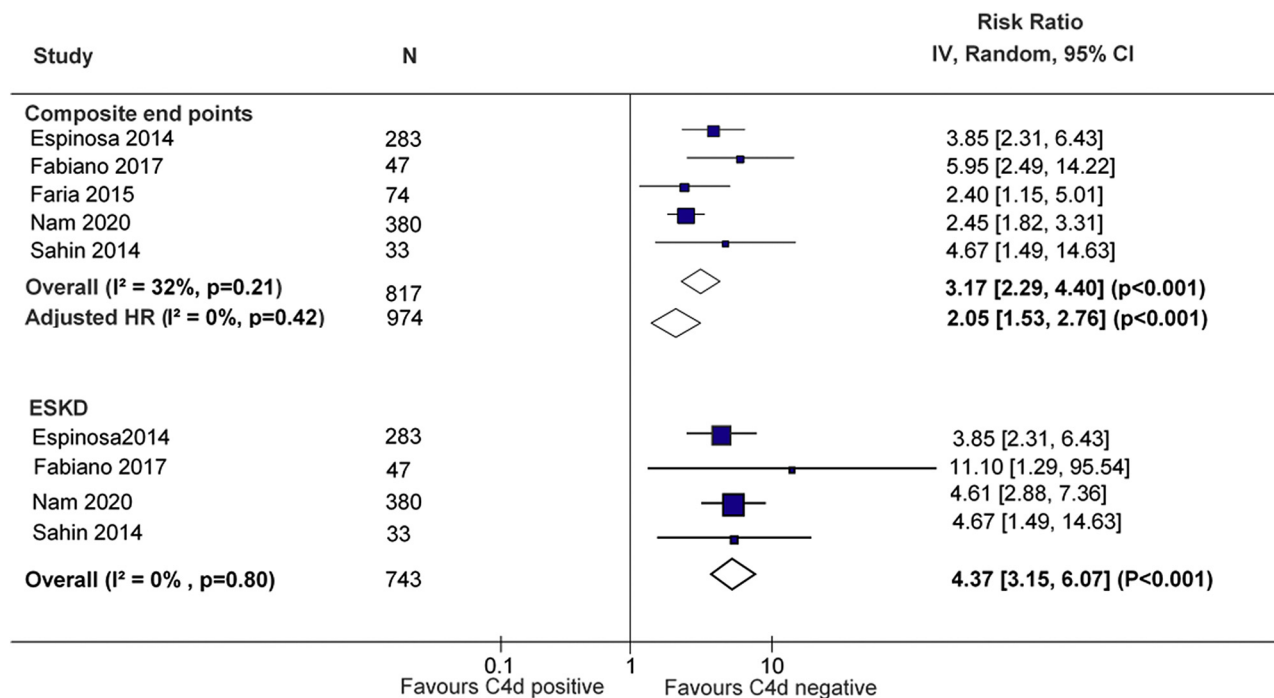


Figure 4. Forest plot for C4d deposits on the kidney progression events (end-stage kidney disease [ESKD] and composite kidney progression events). Composite kidney progression events, >30% decline in estimated glomerular filtration rate (eGFR) or ESKD. Adjusted hazard ratio (HR), 5 studies with 974 patients were analyzed by adjusted HR.

studies^{9,12,16,21,22} with 974 patients), glomerular C4d deposition was an independent risk factor for IgAN progression (hazard ratio [HR], 2.05; 95% CI, 1.53-2.76; $P < 0.001$; $I^2 = 0\%$; $P = 0.42$; Fig 4). We further conducted sensitivity analysis using a hard end point of 50% eGFR decline or ESKD. We found that C4d was still an independent risk factor for IgAN (RR, 4.06; 95% CI, 3.06-5.41; $P < 0.001$; $I^2 = 0\%$; $P = 0.54$).

We also performed subgroup analysis according to stage of chronic kidney disease or proteinuria, with similar results for glomerular C4d deposits across chronic kidney disease stages. Importantly, glomerular C4d deposition was an independent risk factor for kidney progression in the early stage of IgAN with a mean eGFR ≥ 90 mL/min/1.73 m² (HR, 2.52; 95% CI, 1.12-5.70; $P = 0.03$; Fig S2).

DISCUSSION

Glomerular deposition of C4d is a widely used biomarker for complement lectin pathway activation in IgAN. In this meta-analysis of studies comprising 1,251 patients and 199 kidney events, we evaluated the association of glomerular C4d deposition and IgAN disease severity. The findings support that glomerular C4d deposition is strongly associated with high proteinuria, hypertension, and decreased GFR. Patients with C4d deposition exhibited more severe kidney lesions on biopsy, including M1, E1, S1, and T1/2 lesions, according to the

Oxford classification score. In pooled multivariate analysis, glomerular C4d was a strong independent risk factor for the development of kidney failure, even in patients with an early stage of IgAN. These results suggest that glomerular C4d deposition may serve as a stable biomarker of kidney progression.

Complement activation has a role in the development and progression of IgAN. IgA1 can activate both the lectin and alternative pathways in vitro and pathway components are present in mesangial deposits, including properdin and factor H in the alternative pathway and mannan-binding lectin, mannan-binding lectin-associated serine proteases 1 and 2, and C4d in the lectin pathway. Recent studies suggest that complement factors and their fragments in serum, urine, or kidney tissue may serve as biomarkers of IgAN; however, most have not yet been validated.

In this meta-analysis including 8 studies of non-Asian populations and 4 studies of Asian populations, we found that approximately one-third of patients had glomerular C4d deposition. Moreover, pooled analysis demonstrated that glomerular C4d was consistently associated with an adverse prognosis in IgAN. Interestingly, the proportion of C4d deposits in the Asian populations was higher than that in the non-Asian populations, suggesting that more patients in the Asian population experience lectin pathway complement activation. This is consistent with the finding of increased proportions of inflammatory lesions (endocapillary hypercellularity and/or the presence

of crescents) and higher risk for ESKD progression in Asian populations with IgAN than in non-Asian populations with IgAN.²⁴

However the definitions of C4d positivity in different studies were inconsistent. In Asian cohort studies, the definition of C4d positivity was reported as C4d deposition > 50%^{10,11} or >25% of nonsclerotic glomeruli.²¹ In non-Asian cohorts, the definition reported as C4d deposition was >75%,^{12,13} >50%,^{16,22} or >25% of nonsclerotic glomeruli.¹⁴ Thus, whether the difference in C4d deposition between Asian and non-Asian populations was the result of different race or the definition needs further investigation. Also, C4d deposits were more common in severe cases of IgAN including heavier proteinuria or decreased GFRs; thus, patient selection bias may also have influenced the reported prevalence.¹⁴

In transplant kidney biopsy specimens, staining of C4d is a long-lasting marker that identifies sites at which antibodies have bound to the graft endothelium and activated complement. Additionally, it is a potential diagnostic tool for C3 glomerulonephritis or thrombotic microangiopathy.^{25,26} In the present study with more than 1,000 patients, we confirmed that glomerular C4d staining can also be used as a stable biomarker for disease progression in IgAN.

However, before it is used in clinical practice, a number of issues need to be resolved. First, there is still no uniform definition of glomerular C4d positivity. We observed that the definition of C4d staining positivity varied among studies, including C4d deposition in >25%, >50%, >75%, or any of nonsclerotic glomeruli. Second, different methods of glomerular C4d staining were used in different studies. Third, most studies were retrospective, and prospective cohort studies are still needed to inform the clinical use of this biomarker. The origin of C4d deposition in IgAN is unclear; it is speculated that C4d is the result of lectin pathway activation because C1q is always negative in IgAN. However, IgG can be found in the mesangial area of glomerulus in IgAN using immunofluorescence or much higher in spectrometry analysis. The cause of C4d deposition requires further investigation in future studies.

Our study provides comprehensive evidence of glomerular C4d deposition as a potential useful biomarker in IgAN. This study benefits from a volume of data from different populations and the rigorous methodology used.

However, our study has several limitations. The major limitation of the study is that it was mainly based on small studies with limited sample sizes and end point events, without a similar method or definition of C4d staining. Second, most studies involved non-Asian populations. More data from Asian populations were still needed because this disease is most common in Asian patients. Finally, we only evaluated the role of glomerular C4d deposits without analysis of C4d deposition at other sites. A recent study showed that glomerular C4d and arteriolar C4d are both associated with kidney outcomes but that the latter has a stronger association with progressive kidney

disease than the former.²⁷ Also we could not evaluate whether the C4d deposits could predict patient response to immunosuppressive therapy. Thus, more studies are needed to investigate C4d deposits in arterioles and associations with progression in IgAN.

In conclusion, our study provides strong evidence that glomerular C4d deposits are associated with adverse clinical and pathologic characteristics and are an independent risk factor for kidney failure in IgAN. These results suggest that glomerular C4d can be a potentially useful biomarker for predicting prognosis in IgAN. Future studies should evaluate whether the addition of C4d deposition improves the predictive power of the International IgAN Prediction Tool.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Subgroup analysis of prevalence of C4d deposition in IgAN (subgroup analysis was performed by age and C4d positive definition).

Figure S2: Subgroup analysis of C4d deposits on the kidney progression events according to stage of CKD or proteinuria.

Table S1: Search strategy.

Table S2: The AHRQ checklist.

Table S3: The NOS.

ARTICLE INFORMATION

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