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C4d, rather than C3d and C5b-9, Is Associated with Graft Loss in Recurrent IgA Deposition after Kidney Transplantation

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Keywords
Complement · Graft survival · Iga nephropathy · Kidney transplantation · Renal biopsy

Abstract

Introduction: Recurrent IgA deposition is common after kidney transplantation. However, it is difficult to define whether IgA deposition is innocuous or contributes to organ damage. Next, although complement is known to be involved in the pathogenesis of IgA nephropathy (IgAN), its involvement has not been studied systematically in kidney transplant recipients (KTRs). ***Methods:*** KTRs with biopsy-proven native IgAN who underwent kidney biopsy after transplantation between 1995 and 2020 were included. Recurrent IgA deposition was defined as IgA deposit in the glomerulus. Staining of complement factors C4d, C3d, and C5b-9 was quantitatively evaluated using ImageScope. ***Results:*** Sixty-seven KTRs (85% male, 46 ± 13 years old, 12 [6–24] months after transplantation, 58% with indication biopsy) were included in the analyses. Of them, 25 (37%) had recurrent IgA deposition. There were no clinical differences between KTR with and without recurrent IgA deposition. C3d and C5b-9 were always present in biopsies with IgA deposition, while C4d was present in 48% of the biopsies. During a median follow-up of 9.6 [4.8–14] years, 18 (27%) KTRs developed death-censored graft failure. Recurrent IgA deposition was not associated with graft failure. Of the evaluated complement factors, only C4d staining was associated with graft failure in KTR with recurrent IgA deposition (hazard ratio = 2.55, 95% confidence interval = 1.07–6.03, $p = 0.034$). ***Conclusions:*** Recurrent IgA deposition was not associated with graft failure in itself. C4d, when present, is strongly associated with graft loss in KTR with recurrent IgA deposition, suggesting a pathogenic role for the lectin pathway in recurrent IgAN.

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Introduction

IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide, characterized by the deposition of IgA in the glomerulus [1–3]. The natural course of IgAN leads to end-stage kidney disease in approximately 13–19% of the patients at 10 years and 33–39% at 20 years after diagnosis [4–7].

IgAN is presumed to be caused by increasing circulatory levels of galactose-deficient IgA1, to which autoantibodies are directed, leading to immune complex formation. Deposition of these immune complexes in the mesangium stimulates mesangial cells to produce pro-inflammatory and pro-fibrotic cytokines and activates the complement system, leading to the amplification of glomerular injury [8]. Initially, complement activation in IgAN was thought to occur solely through the alternative pathway [9, 10]. Later, it was reported that in addition to the alternative pathway, the lectin pathway is also activated in a subset of patients and that these patients exhibited significantly worse kidney function and higher levels of proteinuria [11–13]. Conversely, the classical pathway has consistently been shown to be of lesser importance in the pathogenesis of IgAN [9–12, 14].

Patients with IgAN are ideal candidates for kidney transplantation because they are generally younger and have fewer comorbidities compared to patients with other kidney diseases [15]. However, even after successful transplantation, IgAN recurs frequently in the allograft with a reported incidence of 8–53% [16]. A recent multicenter study revealed that 23% of kidney transplant recipients (KTRs) with biopsy-proven IgAN as their primary kidney disease experienced a recurrence of IgA deposits within 15 years after transplantation, resulting in poorer long-term graft outcomes [17]. Nevertheless, due to the diverse study designs in previous literature, which include protocol and indication biopsies with varying follow-up times, it remains challenging to ascertain whether recurrent IgA deposition in individual KTRs contributes to graft damage. Furthermore, while a number of studies have demonstrated the involvement of complement activation in the native kidney, little is known about the role of the complement system and the activation pathway in KTR with recurrent IgA deposition after transplantation [18, 19]. Therefore, this study aimed to evaluate whether recurrent IgA deposition on posttransplant allograft biopsies is associated with graft survival and to assess the involvement of the complement system, including the activation pathway.

Method

Study Design and Population

All adult KTRs with biopsy-proven IgAN as their primary kidney disease and who underwent kidney biopsy at any moment after transplantation at University Medical Center Groningen (UMCG), The Netherlands, between 1995 and 2020 were included in the study. If a KTR underwent more than one kidney biopsy after transplantation, the first kidney biopsy was used. Relevant information regarding clinical data at the time of transplantation and biopsy was retrieved from the medical records. Delayed graft function was defined as the need for dialysis within the first week after transplantation. Proteinuria is expressed as g/10 mmol creatinine (PCR).

The study end point was death-censored graft failure, defined as the need for re-transplantation or (re-) initiation of dialysis. The end point was recorded until October 2022. One KTR was lost to follow-up after 4.2 years, and this KTR was censored at that time. Since 2015, in the extension of the ongoing TransplantLines Biobank and Cohort study [20], the Institutional Review Board (IRB) of the UMCG gives an exemption from requiring written informed consent for studies that use clinical data and leftover material of all KTR in UMCG, upon approval of the study protocol (METc 2014/077). The current study has been registered and approved by the IRB of the UMCG (research register number: 201700880) and was conducted in accordance with the World Medical Association Declaration of Helsinki and the Declaration of Istanbul. This study was described following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000540986) [21].

Biopsy Evaluation

The routine diagnostic laboratory performed Immunofluorescent IgA staining using BenchMark Ultra automated immunostainer. An experienced nephropathologist (MCvdH) evaluated the IgA staining deposition in the glomeruli. Recurrent IgA deposition was defined as the presence of IgA staining in the glomeruli. For biopsies with recurrent IgA deposition, the MEST-C score (mesangial hypercellularity [M], endocapillary hypercellularity [E], segmental sclerosis [S], tubular atrophy/interstitial fibrosis [T], and glomerular crescent [C]) according to the Oxford classification was retrieved from the biopsy reports [22].

Complement Staining in Kidney Biopsies

Frozen kidney biopsies were cut into four-µm-thick sections. Fixation of the kidney section was done using cold acetone (−20°C) for 10 min. The stainings of complement factors C4d, C3d, and C5b-9 were performed by immunohistochemistry technique using in-house stainings with the following primary antibodies: polyclonal rabbit anti-human C4d (BI-RC4D, Biomedica, Vienna, Austria); polyclonal rabbit anti-human C3d (A0063, DAKO, Carpinteria, CA, USA); monoclonal mouse anti-human C5b-9 (M0777, DAKO, Carpinteria, CA, USA) [23]. Solutions were prepared with BSA (A9647, Sigma, St Louis, United States) and phosphate-buffered saline (17-512Q, Lonza, Wijchen, The Netherlands). Kidneys from deceased donors were used as a positive control. Additional positive control of kidney biopsy from a KTR with antibody-mediated rejection was used for C4d staining. For the negative control, the first staining antibody was replaced with phosphate-buffered saline. The detailed staining protocol is described in online supplementary Table 2. To avoid day-to-day variation and allow for comparison between biopsies, all stainings per complement factor were performed on the same day, with the same reagents, antibody dilutions, and incubation times.

Stained slides were digitalized using a Hamamatsu slide scanner (Hamamatsu Photonics, Hamamatsu, Japan) and analyzed in the Aperio ImageScope software (Leica Biosystems, Nussloch, Germany). Quantitative scoring was performed by calculating the percentage of positive pixels in all glomeruli in each biopsy using the Positive Pixel Count v9 algorithm. For this, the threshold for positivity was tuned in the negative control so that the percentage of positive pixels in each glomerulus in the negative control was 0.00%. We used the default setting from the Positive Pixel Count v9 algorithm, except for the following input parameters: (1) hue value, where we changed the value from 0.1 to 0.0 because we used red color from 3-Amino-9-ethylcarbazole to show positivity; (2) hue width, where we tightened the color band from 0.5 to 0.1 so that the color spectrum that was deemed positive was more specific; (3) upper limit of intensity (Iwp[High]), where we changed the threshold from 220 to 255 so that capillary lumen in the glomerulus will also be considered as a negative pixel; and (4) color saturation threshold, where we tried various thresholds to ascertain that the percentage of positivity of all glomerulus in the negative control was 0.00%. The detailed input parameters for the algorithm are described in the Positive Pixel Count Algorithm user's guide. After the threshold had been set, all biopsies of one complement factor staining were quantified using the same threshold settings. The percentage of positivity used for the analyses was derived from the median percentage of all glomeruli in the biopsy. An example of positive pixel quantification is presented in online supplementary Figure 1.

Statistical Analyses

Data distribution of continuous variables was assessed by Quantile-Quantile plots. For descriptive statistics, continuous variables were presented as mean ± standard deviation for variables with normal distribution and as median interquartile range for variables with skewed distribution. Categorical variables were expressed as numbers (valid percentages). Differences in clinical characteristics among subgroups of KTR according to the recurrent IgA deposition status were tested by independent *T* test for continuous variables with normal distribution, Mann-Whitney U test for continuous variables with skewed distribution, and χ^2 for categorical variables.

For the prospective analyses, Cox proportional-hazard regression analyses were performed to assess the associations of the IgA deposition and the percentage of complement factors staining positivity with graft failure. All data were analyzed using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). For all analyses, a two-sided p value <0.05 was considered statistically significant.

Results

Sixty-seven KTRs with biopsy-proven IgAN as the primary kidney disease were included in the analyses (online suppl. Fig. 2). The majority of the KTRs were male, with a mean age of 46 years. The median time of biopsy was 12 [6–24] months after transplantation, and 58% underwent a biopsy due to clinical indications (Table 1). The timing of the biopsy in each KTR is visualized in online supplementary Figure 3.

Among the 67 included biopsies, 25 (37%) had recurrent IgA deposition. There were no differences in baseline characteristics between KTR with and without recurrent IgA deposition (Table 1). IgA deposition was observed in the mesangium in 1 (4%), in the GBM in 14 (56%), and in both mesangium and GBM in 10 (40%) biopsies. All biopsies except 1 could be evaluated for the MEST-C score. Of them, 19 (79%) had a MEST-C sum score of 0, 1 (4%) had a MEST-C sum score of 1, 3

Table 1. Characteristics of the study population

Variables	Total (*N* = 67)	No recurrent IgA deposition (*N* = 42)	Recurrent IgA deposition (*N* = 25)	*p* value
Baseline characteristics				
Female sex, *n* (%)	9 (13)	6 (14)	3 (12)	1.0
First transplantation, *n* (%)	61 (91)	39 (93)	22 (88)	0.8
Preemptive transplantation, *n* (%)	15 (22)	8 (19)	7 (28)	0.6
BMI at transplantation, kg/m^2	25.8±3.9	25.9±3.8	25.9±4.2	1.0
Cold ischemia time, h	4 [2.4–15]	8.8 [2.4–14.7]	3.1 [2.5–15]	1.0
Delayed graft function, *n* (%)	14 (21)	12 (29)	2 (8)	0.091
Total HLA mismatch	3 [2–3]	3 [2–3]	3 [2, 3]	0.5
Pretransplant DSA, *n* (%)	0 (0)	0 (0)	0 (0)	1.0
Induction therapy, *n* (%)				0.3
No	19 (28.4)	10 (23.8)	9 (36)	
Basixilimab/daclizumab	46 (68.7)	30 (71.4)	16 (64)	
Anti-thymocyte globulin	2 (3.0)	2 (4.8)	0 (0)	
Living donor, *n* (%)	32 (48)	17 (41)	15 (60)	0.2
Female donor, *n* (%)	39 (58)	22 (52)	17 (68)	0.3
Donor age, years	49±13	49±14	49±12	0.9
Clinical characteristics at the time of biopsy				
Age at biopsy, years	46±12	48±12	44±13	0.3
Time after transplantation, months	12 [6–24]	12 [5–23]	12 [8–42]	0.3
De novo DSA, *n* (%)	1 (1.6)	1 (2.4)	0 (0)	1.0
eGFR, mL/min/1.73 m^2	39.3±18	36.6±15.8	43.8±21.1	0.1
Proteinuria/creatinine ratio, g/10 mmol	0.21 [0.09–0.37]	0.24 [0.07–0.38]	0.18 [0.11–0.30]	0.8
Indication biopsy, *n* (%)	39 (58)	25 (60)	14 (56)	1.0
Cellular rejection, *n* (%)	14 (21)	10 (25)	4 (16)	0.6

BMI, body mass index; DSA, donor-specific antibody; eGFR, estimated glomerular filtration rate based on the creatinine-based CKD-EPI 2009 formula; HLA, human leucocyte antigen. *Body mass index at transplantation was missing in 5 patients, proteinuria/creatinine ratio was missing in 3 patients, cold ischemia time was missing in 2 patients, pretransplant DSA was missing in 1 patient, de novo DSA was missing in 3 patients, and total human leucocyte antigen mismatch was missing in 7 patients.

(13%) had a MEST-C sum score of 2, and 1 (4%) had a MEST-C sum score of 3. All of the biopsies with MEST-C sum score ≥1 were from the indication biopsy group.

Quantification of complement factors staining revealed that glomerular C3d but not C5b-9 positivity was higher in biopsies with recurrent IgA deposition compared to biopsies without recurrent IgA deposition (Fig. 1). When stratified based on the biopsy types, both C3d and C5b-9 positivity were significantly higher in biopsies with recurrent IgA deposition in indication biopsy groups but not in the protocol biopsy groups (Fig. 1). Furthermore, C3d and C5b-9 deposition closely followed the IgA deposition pattern. On the contrary, glomerular C4d staining was present in a number of biopsies, irrespective of IgA deposition (48% in the recurrent IgA group vs. 43% in the nonrecurrent group, *p* value = 0.9). The percentage of glomerular C4d positivity was similar between biopsies with and without recurrent IgA deposition (Fig. 1). Moreover, C4d was predominantly deposited in the mesangium. One biopsy revealed C4d staining in the peritubular capillaries; however, this patient did not have recurrent IgA deposition (online suppl. Fig. 4). Representative figures of IgA and complement factor C4d, C3d, and C5b-9 stainings are presented in Figure 2.

Prospective Analyses

The median follow-up after kidney transplantation was 10.9 [7.4–15.3] years, and after kidney biopsy, it was 9.6 [4.8–14.0] years. During follow-up, 8 (12%) KTR died with functioning grafts, and 18 (27%) KTR experienced graft failure. Graft failure occurred in 3 out of 28 (11%) KTRs who underwent protocol biopsy; however, none of these KTRs had recurrent IgA deposition. Among 39 KTRs who underwent indication biopsy, 7 out of 14

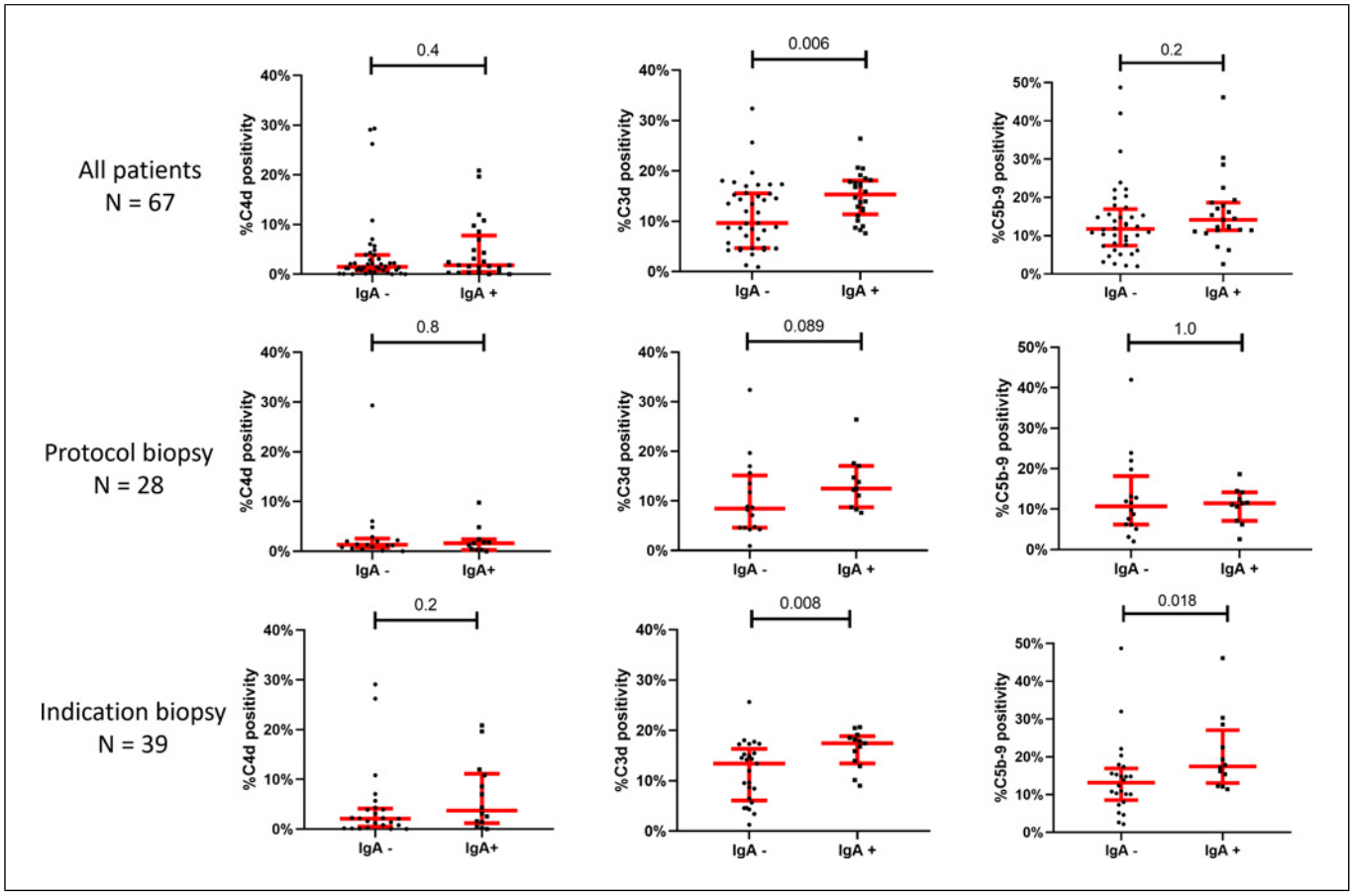

Fig. 1. Comparison of glomerular positivity percentage of complement factors staining in kidney transplant recipients based on the IgA deposition status. Mann-Whitney U test was used for the statistical analysis.

(50%) of KTRs with recurrent IgA deposition and 8 out of 25 (32%) of KTRs without recurrent IgA deposition experienced graft failure (online suppl. Fig. 5). Cox-regression analysis revealed that the risk of developing graft failure was similar between those with and without recurrent IgA deposition in KTR with indication biopsy (hazard ratio [95% confidence interval] = 1.91 [0.69–5.31], p = 0.2).

For the complement factors, the percentage of glomerular C4d positivity was significantly associated with an increased risk of graft failure in KTR with recurrent IgA deposition who underwent indication biopsy (hazard ratio [95% confidence interval] = 2.55 [1.07–6.03], p = 0.034). On the contrary, either C3d or C5b-9 was not associated with an increased risk of developing graft failure in these KTRs (Fig. 3a). In KTR without recurrent IgA deposition, none of the complement factors were associated with graft failure (Fig. 3b).

Discussion

In this single-center cohort of KTR with biopsy-proven IgAN as the primary kidney disease, the incidence of recurrent IgA deposition was 37% at the median time of 12 [6–24] months after transplantation. However, recurrent IgA deposition was not associated with an increased risk of graft failure. The percentage of positivity of glomerular C3d and C5b-9 but not C4d was higher in KTR with recurrent IgA deposition who underwent indication biopsy compared to those without recurrent IgA deposition. Nevertheless, glomerular C3d and C5b-9 positivity was not associated with an increased risk of graft failure regardless of the presence of IgA deposition; conversely, glomerular C4d positivity was associated with an increased risk of graft failure in KTR with but not without recurrent IgA deposition.

Younger age at transplant, living donor, presence of DSA, and preemptive transplantation have been

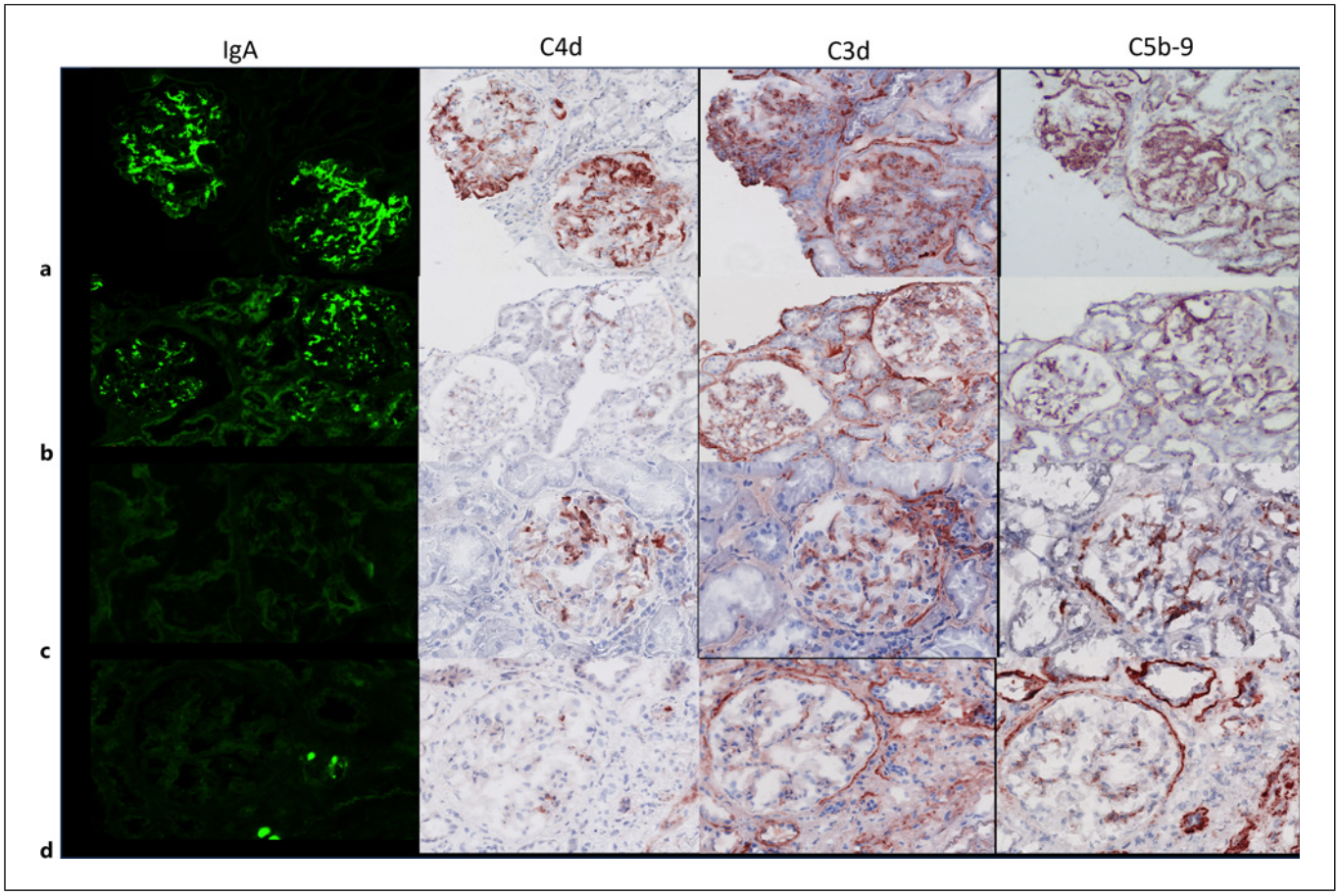

Fig. 2. IgA and complement factors staining in the kidney biopsy of kidney transplant recipients with positive for IgA and C4d (**a**), positive for IgA but negative for C4d (**b**), negative for IgA but positive for C4d (**c**), negative for IgA and C4d (**d**).

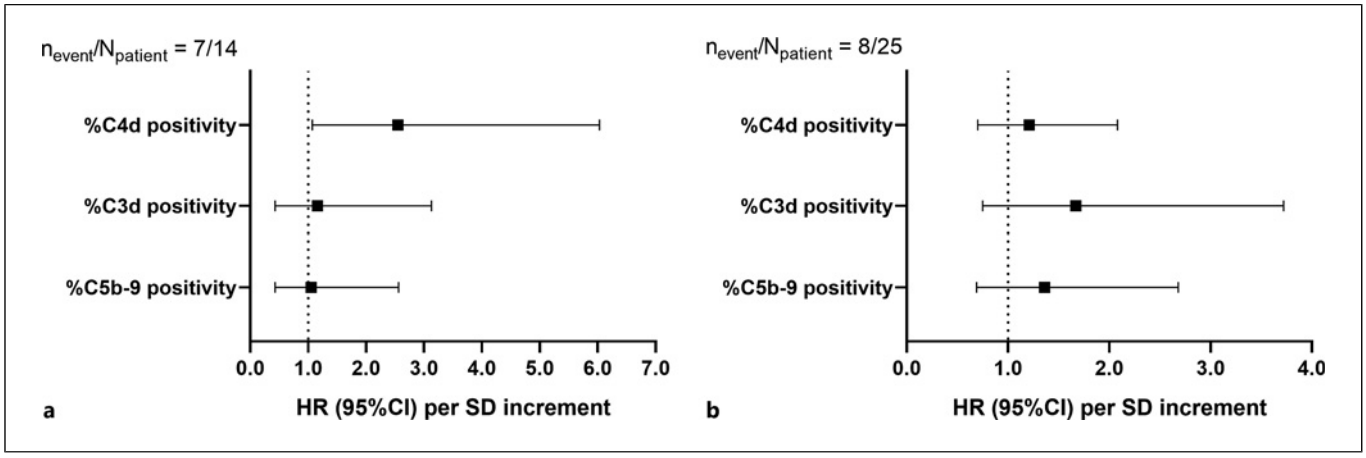

Fig. 3. Forrest plot for the association of complement factors staining positivity in the glomeruli with death-censored graft failure in kidney transplant recipients who underwent indication biopsy. **a** KTR with recurrent IgA deposition. **b** KTR without recurrent IgA deposition. The HR (95% CI) was from the crude Cox-proportional hazard regression analysis. CI, confidence interval; HR, hazard ratio; SD, standard deviation.

previously reported as independent risk factors for IgA recurrence after transplantation [17, 24, 25]. However, we did not find differences between KTR with and without recurrent IgA deposition in our study population. Next to that, we found no difference in graft survival when stratified based on the presence and absence of recurrent IgA deposition. Previous studies reported conflicting findings, whereas some studies found that the incidence of graft loss was similar between KTR with and without recurrent IgA deposition [26–28], and others found that the incidence of graft loss was greater in KTR with recurrent IgA deposition [17, 29–31]. In a recent systematic review and meta-analysis study of recurrent IgA deposition after transplantation, it is reported that there is a publication bias in regard to the graft outcome [32]. Thus, additional studies are still needed to confirm whether recurrent IgA deposition in itself contributes to graft damage.

In native IgAN, patients with mesangial and GBM deposition have more severe histological changes and have higher levels of proteinuria at the time of biopsy than patients with only mesangial deposition. Furthermore, these patients are also more likely to develop progressive kidney disease [33–36]. Because of that, GBM deposition is considered an important prognostic factor in native IgAN [33–36]. IgA deposition in the GBM alongside mesangium in KTR with recurrent IgAN has been reported previously [37, 38]; however, it has not been evaluated systematically. Since we only have 1 biopsy without GBM deposition in the current study, we could not evaluate whether GBM deposition of IgA is also an important prognostic factor in the posttransplant setting.

A previous study has shown that glomerular C3 deposition was significantly more prevalent in KTR with recurrent IgA deposition than in KTR with nonrecurrent IgA deposition [18]. In a more recent study, C3 deposition was found in all KTR with recurrent IgA deposition [19]. Furthermore, C3 deposition has also been shown to be significantly correlated with the IgA staining intensity [39]. This is similar to our finding, where we found that KTR with recurrent IgA deposition had a higher C3d positivity. C5b-9 also showed similar findings as C3d. However, both glomerular C3d and C5b-9 positivity were not associated with graft failure in KTR with recurrent IgA deposition. This might be explained by the fact that all KTR with recurrent IgA deposition had glomerular C3d and C5b-9 deposition to some extent. Conversely, although glomerular C4d positivity did not differ between KTR with and without recurrent IgA deposition, it was associated with an increased risk of graft failure among KTR with recurrent IgA deposition. Our findings are in line with previous studies that showed that the presence of C4d in KTR with recurrence of IgA was associated with a higher risk of graft failure [24, 40]. This is similar to the findings in native IgAN, where the presence of C4d in the glomerulus is associated with more rapid disease progression and poorer outcomes [41].

While glomerular C4d positivity was associated with an increased risk of graft failure in KTR with recurrent IgA deposition that was not the case in KTR without recurrent IgA deposition. Importantly, C4d deposition was predominantly found in a mesangial pattern in the kidneys with recurrent IgA deposition and none of these patients had DSA, thus making a HLA antibody-mediated activation mechanism improbable.

Findings from previous studies show that the presence of C4d in IgAN is due to complement activation via the lectin pathway and not via the classical pathway [11–13, 40]. However, it remains unclear which factors lead to C4d deposition in IgAN. It has been hypothesized that the activation of the complement system via the lectin pathway depends on the degree of IgA glycosylation [42]. Another hypothesis is that the activation via the lectin pathway is triggered by the injured tissue in the glomerulus secondary to IgA deposition [12]. Nevertheless, these hypotheses are yet to be proven. Despite the lack of current understanding of the pathomechanism behind lectin pathway activation, the significance of glomerular C4d deposition on graft survival suggests that it is an important prognostic marker in recurrent IgAN. Interestingly, mesangial C4d deposition was also detected in a proportion of the biopsies in the absence of IgA deposition. We hypothesize that this could still be a marker of mild IgA deposition below the detection threshold, similar to the situation in antibody-mediated rejection in which C4d is thought to be a maker of IgG-mediated complement activation, though IgG deposition is usually not detected in the biopsy [43].

Currently, there are no specific therapies for recurrent IgAN [44]. Although targeted-release oral budesonide shows promising results in treating patients with native IgAN [45], its efficacy in KTR with recurrent IgAN may be limited, as KTRs are already on steroid treatment [46]. The off-label use of eculizumab, a monoclonal antibody that inhibits complement at the C5 level, has been reported in two cases of recurrent crescentic IgAN and shows conflicting results. The first case reported that the graft loss could not be prevented

[47], whereas the second reported the contrary [48]. Other than eculizumab, a number of anti-complement drugs are currently being investigated in clinical trials [49]. Since our study and previous studies have found that C4d was associated with worse outcomes in KTR with recurrent IgA deposition [24, 40], and that the activation pathway in this disease is likely to be via the lectin pathway [11–13], treatment with anti-complement drugs that target only the lectin pathway might be beneficial.

Several important limitations need to be mentioned. First, this study was performed in a single center in The Netherlands. Second, as this was an observational study, the nature of this study did not allow us to infer causality. Third, though this is one of the larger IgA recurrence cohorts in the literature [32], it is too small for a meaningful multivariable analysis. Lastly, as the beginning of inclusion in our cohort dates back to the nineties, our results could be influenced by variable immunosuppression regimens.

Conclusion

Recurrent IgA deposition is common after kidney transplantation; nevertheless, it was not associated with an increased risk of graft failure in itself. Although the complement system in KTR with recurrent IgA deposition is largely activated via the alternative pathway, only glomerular C4d deposition that is in conjunction with IgA deposition is significantly associated with graft loss. This suggests a pathogenic role for the lectin pathway in recurrent IgAN, and targeting this pathway may have potential therapeutic benefits. Future studies with larger KTR populations are needed to confirm our findings.

Statement of Ethics

The current study has been registered and approved by the IRB of the UMCG (research register number: 201700880) and was conducted in accordance with the World Medical Association Declaration of Helsinki and the Declaration of Istanbul. The IRB of the UMCG exempts studies that use clinical data and leftover material of all KTR in UMCG from requiring written informed consent upon approval of the study protocol.

Conflict of Interest Statement

All authors have no conflict of interest to declare.

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Author Contributions

F.F.A., A.U., J.vdB., and S.P.B. conceived and designed the study. F.F.A., A.U., and R.G.M. retrieved the relevant clinical and laboratory data. F.F.A., G.T., and M.C.vdH. performed the staining. M.C.vdH. and I.M.B. evaluated the biopsy results. I.M.B., M.R.D., J.vdB., and S.P.B. interpreted the findings. F.F.A. wrote the initial draft of the manuscript. All authors revised the manuscript for important intellectual content.

Data Availability Statements

The data that support the findings of this study are not publicly available due to privacy policy and data protection regulations, but it is available from the corresponding author (S.P.B.) upon reasonable request.

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