The clinicopathologic characteristics of Immunoglobulin A nephropathy related to C3 deposits

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Abstract

Background C3 deposits are widely detected in patients with immunoglobulin A nephropathy (IgAN). However, the relationship between the location and intensity of the C3 deposition and prognosis of IgAN is uncertain. Methods 244 patients diagnosed with IgAN were enrolled in our study during 2010- 2016. Patients were divided into groups according to the location of C3 deposits: mesangial area only versus mesangial area and glomerular capillary loops. We also divided those patients into 4 groups according to the intensity of C3 deposition at the base of location. Renal outcomes were end-stage renal disease(ESRD)or a ≥50% reduction in estimated glomerular filtration rate(eGFR), performed by Kaplan–Meier analysis and Cox proportional hazards models. Results Among the 244 recruited patients with IgAN, 139(56.97%) were female. Compared to patients with C3 deposition in the mesangial area only, those with C3 deposition in the mesangial area and glomerular capillary loops had significantly older, lower levels of serum albumin and eGFR, higher levels of uric acid (UA), severe proteinuria, more intense C3 deposits, were more prone to receive corticosteroids and immunosuppression. There were no other significant differences between C3 deposition in the mesangial area only (≤2+ in intensity) group and C3 deposition in the mesangial area and glomerular capillary loops (≤2+ in intensity) group except for age. Patients in C3 deposition in the mesangial area and glomerular capillary loops (>2+ in intensity) group were associated with lower levels of serum albumin, serum IgG and eGFR, higher levels of serum IgM, UA and blood urea nitrogen (BUN),heavier proteinuria and higher interstitial fibrosis/tubular atrophy scores than C3 deposition in the mesangial area deposits only(>2+ in intensity) group. After a median follow-up of 41.86 months,28(11.48%) patients reached the renal outcomes. Higher intensity of C3 deposition in the mesangial area and glomerular capillary loops (95%CI:1.262-76.832, p=0.029) remained an independent risk factor of renal outcomes by multivariate Cox proportional hazards models. Conclusions IgAN patients who had glomerular capillary loops C3 deposits had worse clinical outcomes. Furthermore, the effect of the C3 deposition site on IgA nephropathy is affected by the intensity of C3 deposits.

Background

Immunoglobulin A(IgA) nephropathy (IgAN) is the most common pattern of primary glomerulonephritis worldwide that can progress to renal failure. 10–30% of patients might progress to end-stage renal disease (ESRD) within 20–30 years(1, 2). Therefore, obtaining precise individualized risk estimation and achieving personalized therapy for patients is important. Previous studies have explored valuable clinical risk factors to predict disease progression(2). Among them, massive proteinuria, hypertension, an impaired renal function at baseline were widely recognized(3, 4). Regarding pathological risk factors, the Oxford classification system for IgAN including mesangial hypercellularity (M), segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T), crescent(C) was increasingly used in clinical practice(5–7). However, the Oxford classification system did not include immunofluorescent findings. It is still controversial whether the immunofluorescent features are predictive of outcome in IgAN.

IgAN is defined by mesangial IgA or IgA-dominant immune complex deposition, and 90%–95% of IgAN is accompanied by the C3 deposition (5, 8, 9). The patients with higher-grade mesangial deposition of C3

had worse outcomes than those with lower-grade deposition(10, 11). Some studies had reported that the immune deposits could also be found in glomerular capillary walls and extraglomerular area(12–15). Doi et al. had demonstrated that the location of C3 deposits was associated with the severity of mesangial proliferation(16). Ohsawa et al. had revealed that extra-glomerular C3 (ex-C3) deposition might provide prognostic value in IgAN(13). However, fewer studies explored the relationship between the intensity of C3 deposits and the location in IgAN.

In the study, we compare the baseline findings and follow-up data according to the intensity and location of C3 deposits and investigate its utility as a predictor of renal outcomes in patients with IgAN.

Methods

1. Subjects and Study Design

The patients with renal biopsy-proven IgAN in the Second Xiangya Hospital of Central South University between January 2010 and December 2016 were evaluated for the retrospective study. Our inclusion criteria were renal biopsy-proven IgAN with a minimum of 5 mm of the cortex and 8 glomeruli in the light microscopy sections. And the exclusion criteria were:1. without pathological data or available follow-up data; 2.negative C3 deposition; 3. glomerular capillary loops deposition only;4.with ESRD at the time of biopsy;5.with other glomerular diseases or additional systemic diseases(liver cirrhosis, Henoch-Schönlein purpura, diabetes mellitus, membranous nephropathy, Sjögren's syndrome, antiphospholipid syndrome, gouty nephropathy). 244 remaining patients were enrolled in our study (Fig. 1). Those patients were categorized according to the location into groups: Group A: C3 deposition in the mesangial area only, Group B: C3 deposition in the mesangial area and glomerular capillary loops. According to the significant difference between Group A and Group B in the degree of C3 deposits, those patients were divided into four groups: Group 1：C3 deposition in the mesangial area only and ≤2+ in intensity; Group 2：C3 deposition in the mesangial area and glomerular capillary loops and ≤2+ in intensity; Group 3：C3 deposition in the mesangial area only and ＞2+ in intensity; Group 4：C3 deposition in the mesangial area and glomerular capillary loops and ＞2+ in intensity. Serum IgG was divided into 2 groups according to the cut-off value(9.055mmol/L) of the ROC curve.

2. Clinical and Laboratory Data

We recorded the age, gender, blood pressure, plasma biochemical parameters, urinalysis data, and treatment at the time of renal biopsy from the medical records and retrospectively reviewed. The eGFR was calculated according to the CKD-EPI equation(17). ESRD was defined as eGFR ≤15 ml/min/1.73m^2 or renal replacement therapy（hemodialysis, peritoneal dialysis or renal transplantation）. Hypertension was defined as systolic blood pressure (SBP) ≥140mmHg and(or) diastolic blood pressure (DBP) ≥ 90 mmHg or treatment with antihypertensive drugs. The definition of mean arterial pressure (MAP) was DBP plus one-third of the pulse blood pressure. Microscopic hematuria was defined as＞5 red blood cells per

high-power field in urinary sediment. Hemoglobin <110 g/L in females and <120g/L in males was defined as anemia.

3. Renal Biopsy

All kidney specimens were routinely reviewed by light microscopy, electron microscopy, and immunofluorescence, and evaluated by at least two pathological doctors blinded to patient outcomes (18). Of note, immunofluorescent staining intensity was graded semiquantitatively from 0 to 4, including 0, 1+, 2+, 3+,4+. We determined the location of C3 deposits by IF (mesangial area and glomerular capillary loops). All histology sections were defined according to the new version of Oxford classification: mesangial hypercellularity, a mesangial score of ≤0.5 or ≤50% of glomeruli with ≥4 mesangial cells per mesangial area(M0), a mesangial score of >0.5 or >50% of glomeruli with ≥4 mesangial cells per mesangial area(M1);endocapillary hypercellularity, absent (E0) or present (E1);segmental glomerulosclerosis or tuft adhesions, absent (S0) or present (S1),T0/T1/T2 as the degree of tubular atrophy/interstitial fibrosis (<25%, 25–50%, >50%),C0/C1/C2 as the percentage of glomeruli with cellular or fibrocellular crescents(absent, < 25% of glomeruli, and > 25% of glomeruli).

4. Renal Outcomes

We defined the study outcomes as a≥50% reduction in eGFR or ESRD.

5. Statistical Analyses

The measurement data conformed to the normal distribution by means ± SD. The comparison between groups was performed by t-test. The non-normal distribution data was represented by M (1/4, 3/4). The nonparametric rank-sum test was used for comparison between groups. Survival analysis was performed using the Kaplan-Meier method and compared by a log-rank test. The risk ratio (HR) was calculated using the Cox proportional hazard model, and the impact of C3 deposition intensity and deposition sites on prognosis were analyzed by a multivariate Cox proportional hazard model for IgAN patients. Statistical analysis was performed using SPSS 22.0 software. Two-sided test $P<0.05$ was considered statistically significant.

Results

1. Study Population

A total of 1008 patients with biopsy-proven IgAN were recruited from January 2010 to December 2016 in our center. Of these,141 patients without available pathological biopsy data,390 patients without C3 deposition and 10 patients with C3 deposition in capillary loops only were excluded. We also excluded 45 patients who were with other glomerular diseases or additional systemic diseases.173 patients were lost to follow-up. Two hundred and forty-four patients were ultimately retained for our analysis (Fig. 1).

2. Baseline Characteristics According to the Intensity and Location of C3 Deposits

Clinical, and histological characteristics of patients were described in Table 1 and Table 2. Among the 244 patients investigated,56.97% were female, the mean age was 31.34±0.66 years.198 (81.15%) were categorized as mesangial C3 deposition only (Group A), and the remaining 46(18.85%) as mesangial area and glomerular capillary loops C3 deposition (Group B). Compared with Group A, patients in Group B were significantly older, had higher uric acid (UA), lower serum albumin, eGFR, more severe proteinuria (P = 0.020 and P = 0.0014 and P = 0.003 and P = 0.015 and P = 0.012, respectively). A larger proportion of patients in Group B was treated with corticosteroids or other immunosuppressants (P = 0.002 and P = 0.007, respectively). Notably, the intensity of C3 deposition in Group B was marker than Group A(P = 0.001). To elucidate the relationship between the location and intensity of C3 deposits and renal outcomes, those patients were subdivided into 4 groups according to the intensity of immunofluorescent (Table 2). Interestingly, there was no significant difference in any of the other findings between Group 1 and Group 2 except for age(P = 0.019). Patients in Group 4 presented significantly lower serum albumin and eGFR, more severe proteinuria, higher levels of blood urea nitrogen (BUN)and UA at presentation than those in Group 3(P = 0.016 and P = 0.047 and P = 0.005 and P = 0.008 and P = 0.004, respectively). Serum IgG levels were lower(P = 0.039) but serum IgM levels were higher in Group 4(P = 0.0369) compared with Group 3. Regarding histopathologic features, patients in Group 4 presented with higher interstitial fibrosis/tubular atrophy(T)scores(P = 0.027).

3. C3 Deposition and Renal Outcomes

During a median follow-up of 41.86 (31.61,60.89) months,28(11.48%) patients reached the renal outcomes. Kaplan-Meier analysis revealed that cumulative survival rates were significantly lower in Group B than Group A, Group 4 than Group 3. In regard to other prognosis factors, Kaplan-Meier analysis also suggested that cumulative survival rates were significantly higher in the patients without anemia compared with the patients with anemia, the patients without hypertension compared with the patients with hypertension, the patients without proteinuria compared with the patients with proteinuria, the patients with higher levels of serum IgG compared with those with lower levels of serum IgG, the patients with T0 compared with the patients with T1 or T2, the patients with C2 compared with the patients with C0 or C1. There was no statistically significant difference between non-hematuria and microscopic hematuria and gross hematuria, Group 1 and Group 2, M0 and M1, E0 and E1, S0 and S1 (Figure 1).

4. Univariate and Multivariate Cox Proportional Hazards Models of Risk Factors Associated with Renal Outcomes

In univariate Cox proportional hazards models of our study, blood pressure, levels of hemoglobin, serum albumin, serum creatinine (Scr), BUN, UA, triglyceride (TG), cholesterol (CHOL), serum IgG, eGFR,24-hour urinary protein and T scores, C scores, C3 deposition were associated with renal survival. In multivariate Cox proportional hazards models, SBP(95%CI:1.051–1.200,p = 0.001),serum albumin(95%CI:0.504–0.810,p<0.001),24-hour urinary protein(95%CI:0.376–0.837,p<0.005), eGFR(95%CI:0.863–0.947,p<0.001), TG(95%CI:1.302–2.276,p<0.001), CHOL(95%CI:0.034–0.362,p<0.001), T scores(1.236–84.954,p = 0.031), higher intensity of C3 deposition in the mesangial area and glomerular capillary loops (95%CI:1.262–

76.832,p = 0.029) were independent risk factors. The univariate and multivariate Cox proportional hazards models' results were showed in Table 3.

Discussion

This was a retrospective study. It appeared that IgAN patients who had glomerular capillary loops C3 deposits had a worse clinical outcome. No marked statistical differences were noted among the groups when the intensity of C3 deposition was weaker except for age. However, when the degree of deposits was a marker, the location of C3 deposits was associated with worse renal outcomes. In our study, SBP, serum albumin, 24-hour urinary protein, eGFR, TG, CHOL, T scores were independently associated with poor renal outcomes in patients with IgAN. And C3 deposition in the mesangial area and glomerular capillary loops with higher intensity also remained as a significant predictor of renal outcomes.

The clinical symptoms and the prognosis of IgAN showed quite variable, ranging from asymptomatic hematuria to rapid and irreversible renal failure(19, 20). So, identifying which patients with IgAN will develop progressive renal failure is necessary. Traditional independent risk factors such as SBP, proteinuria, eGFR, MEST-C were confirmed in our study. The T scores were recognized as the most important predictor of developing ESRD, while the roles M, E and S played were controversial (21). And recently several studies had shown that C scores were significantly associated with an unfavorable renal prognosis(5, 22, 23). In our study, M, E, and S had no significant effects on the risk of ESRD. The C scores were not significant in predicting prognosis by multivariate Cox proportional hazards models, most likely because the number of patients with an eGFR of <30ml/min/1.73m^2 was small. Liu et al. showed that a decreased serum IgG level may be an early predictor of poor survival in IgAN patients(24). Consistent with that report, we found lower levels of serum IgG were associated with poor renal outcomes but there was no significant difference after adjusting to multiple risk factors. It was possible because our study subjects were simply grouped by the cut-off value of ROC. Zhao et al. reported that patients with lower levels of time-average albumin were less likely to achieve remission(25). In patients with normal renal function at the time of diagnosis, hypertriglyceridemia was an independent risk factor for the progression of IgAN(26). A possible mechanism involved was that hypertriglyceridemia induced the activation of the PKC pathway which could result in proteinuria by damaging the glomerular capillary barrier(27).

C3 is frequently involved in the formation of immune deposits in IgAN patients, suggesting that complement activation may play a key role in the pathogenesis of IgAN(28–30). In a recent study of Iranian patients, mesangial C3 deposition had a significant correlation with serum creatinine level, crescent formation, endocapillary hypercellularity, segmental sclerosis, mesangial widening and thickening of Bowman's capsule(31). Similarly, a recent study found that the proportion of patients progressing to kidney failure was significantly higher in patients with moderate-severe mesangial C3 staining(11). Interestingly, in a study of Korean patients, a lower concentration of serum C3 correlated with a higher grade of mesangial C3 deposition, and each finding predicted a higher risk of progression to ESRD(10).

Recently, attention was directed toward the association with the location of immune deposits and unfavorable outcomes in patients with IgAN. The patients with IgA deposits along capillary walls showed heavier proteinuria, more severe histologic damage, and were more likely to progress to ESRD(14). Dong et al. demonstrated that immune deposits in the mesangial area and peripheral capillary walls definitively influenced renal outcomes in IgAN not co-deposition of IgG(15). Doi et al. suggested that the location of C3 immune deposits associated with the severity of histologic alterations(16). Masanori et al. showed that hematuria or proteinuria was often observed in patients with the mesangial area and glomerular capillary loops C3 deposition. And the greater the degree of C3 deposits, the higher the histological activity. But they observed this only in pediatric patients(32). Also, Ohsawa et al. indicated that IgAN patients with extraglomerular (Bowman's capsule and/or arteriole) C3 deposits had an adverse outcome. And they made a specific assumption that the ex-C3 deposition might be related to not only the immune system but also metabolic regulation(13). Consistent with previous reports, C3 deposits in the mesangial area and glomerular capillary loops showed a distinct association with poor renal outcomes in our study. A more important finding is that in the greater degree of C3 deposits, the deposition pattern of mesangial area and glomerular capillary loops were associated with more severe proteinuria and worse renal outcomes. Such a result was not evident in the weaker degree of C3 deposits. These findings demonstrate that the effect of the deposition site on IgAN is affected by the intensity.

Our study had some limitations that warrant mention. First, the retrospective study limited the findings of our research. Second, altering the treatment plan during the follow-up did not be taken into account. Third, several patients were without pathological data and lost to follow-up, resulting in a bias. Fourth, we excluded the samples with capillary loops deposition only due to a small number, which cannot identify the impact of these samples on the vascular lesion.

In conclusion, we found that IgAN patients in groups with the mesangial area and glomerular capillary loops C3 deposits showed more severe clinical and pathological alterations than those with the mesangial area only C3 deposits. Furthermore, the effect of the C3 deposition site on IgAN is affected by the intensity of C3 deposits.

Abbreviations

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; BUN, blood urea nitrogen; UA, uric acid; TG: triglyceride; CHOL, cholesterol; Ig, immunoglobulin; C3, complement 3; C4, complement 4; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; M, mesangial hypercellularity; S, segmental sclerosis; T, interstitial fibrosis/tubular atrophy, C,crescent;M0, mesangial hypercellularity score of ≤0.5; M1, mesangial hypercellularity score 0.5; E0, absence of endocapillary hypercellularity;E1, presence of endocapillary hypercellularity; S0, absence of segmental glomerulosclerosis; S1, presence of segmental glomerulosclerosis; T0, tubular atrophy/interstitial fibrosis ≤25% of cortical area; T1, tubular atrophy/interstitial fibrosis 26–50% of cortical area; T2, tubular atrophy/interstitial fibrosis50% of

cortical area.C0, no crescent in glomeruli; C1, crescent in < 25% of glomeruli, C2, crescent in > 25% of glomeruli.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Second Xiangya Hospital, Central South University. We obtained informed written consent from all participants involved in our study.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Hong Liu and Lingzhi Wu contributed to the design and concept of the study. Lingzhi Wu, Di Liu, Jing You, Xiaofang Tang, Ming Xia performed the experiments. Lingzhi Wu, Guo chun Chen, Yu Liu, Xuejing Zhu analyzed the data. Lingzhi Wu wrote the paper.

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Tables

Due to technical limitations, the Table(s) are only available as a download in the supplemental files section.

Figures

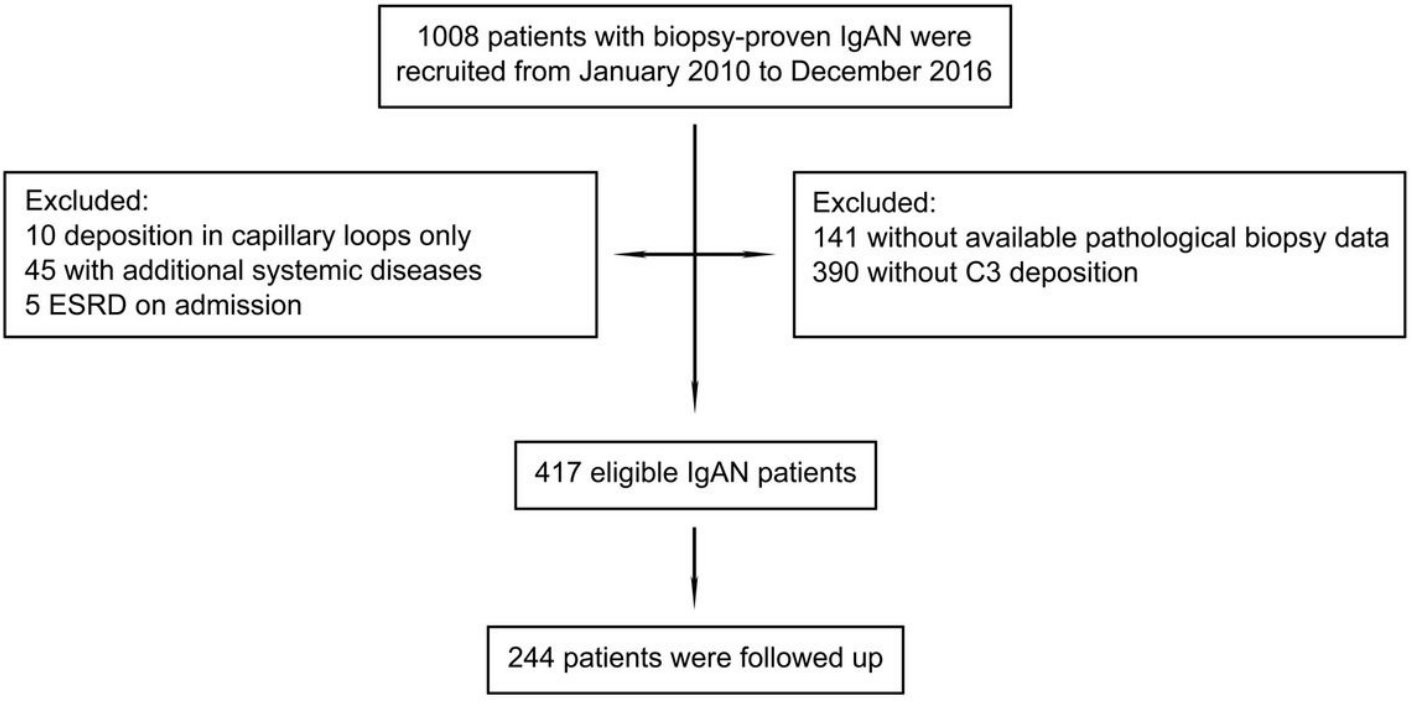

Figure 1

Derivation of the cohort. Abbreviations: IgAN, immunoglobulin A nephropathy; ESRD, end-stage renal disease.

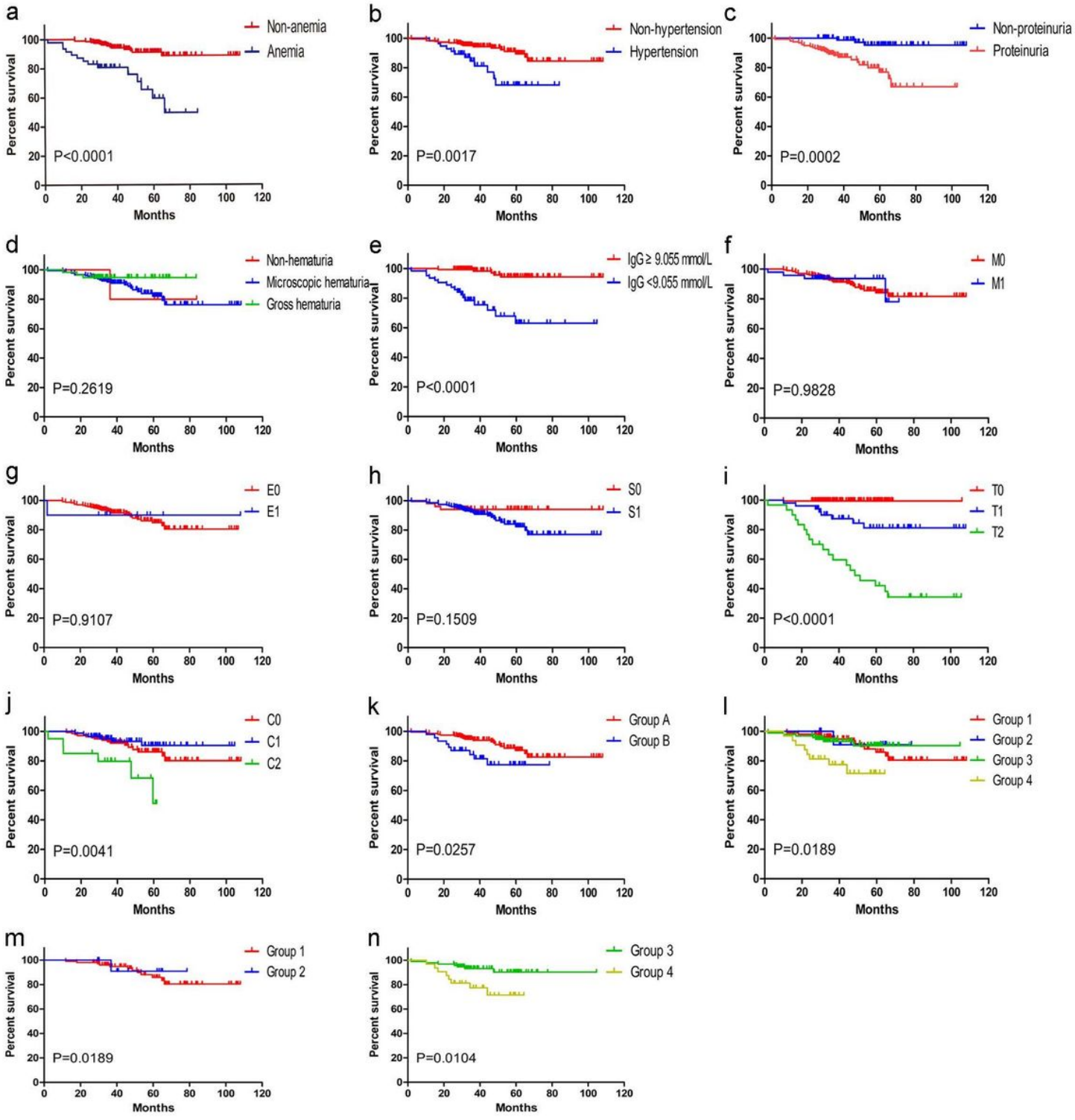

Figure 2

Kaplan–Meier analysis of cumulative survival rates of patients with IgAN according to risk factors. Abbreviations: M0, mesangial hypercellularity score of ≤0.5; M1, mesangial hypercellularity score 0.5; E0, absence of endocapillary hypercellularity;E1, presence of endocapillary hypercellularity; S0, absence

of segmental glomerulosclerosis; S1, presence of segmental glomerulosclerosis; T0, tubular atrophy/interstitial fibrosis ≤25% of cortical area; T1, tubular atrophy/interstitial fibrosis 26–50% of cortical area; T2, tubular atrophy/interstitial fibrosis50% of cortical area.C0, no crescent in glomeruli; C1, crescent in < 25% of glomeruli, C2, crescent in > 25% of glomeruli.

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