

Clinical and prognostic significance of PMN in children with glomerular C1q deposition

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Abstract

Background

Currently, studies to date in MN are consistent with complement activation has an essential role in mediating renal injury, and the LP is considered to be the principal pathway in PMN. CP activation initiated by C1q which deposits are suggestive of SMN. However, C1q deposition together with IgG and C3 granular deposit is found in many cases of PMN. Currently, the clinical and prognostic significance of C1q deposition in PMN is unclear. Therefore, we conduct this single-center research to explore the clinical and prognostic significance of C1q deposition in children with PMN.

Method:

73 patients with C1q deposition were enrolled in this study. According to the “Case-control matching principle”, 73 patients without C1q deposition during the same period of the renal biopsy were selected as a control group. The clinical and pathological characteristics, treatment response, and long-term renal prognosis were compared between patients with and without C1q deposition.

Result

A total of 146 pediatric patients with PMN included with 86 men(58.9%) and 60 women (41.1%). The median age at onset was 15.0 (14.0–16.0) years. During an average follow-up of 52.4 ± 35.6 months, 8 patients (5.5%) progressed ESKD, 12 (8.2%) patients developed ESRD or renal dysfunction. The frequency of glomerular C4 deposits in the C1q deposits group was significantly higher than no C1q deposits group (34.2% vs 5.5%, $p = 0.000$). There were no other distinct differences in clinical and pathological characteristics between the two groups. Glomerular IgG subclasses were available in 79 patients, there was no difference in the glomerular IgG subclass distribution between the two groups ($p_{IgG1}=0.468, p_{IgG2}=1.000, p_{IgG3}=0.988, p_{IgG4}=0.216$). The Kaplan-Meier survival analysis found that there was no difference in the renal survival of ESRD ($p = 0.415$) and a combined event of ESRD and/or renal dysfunction ($p = 0.214$) between the two groups. The logistic regression analysis ($p = 0.553$) and Cox regression analysis ($p = 0.618$) revealed that C1q deposition failed to associate with renal dysfunction.

Conclusion

The CP does occur in some patients of PMN. However, it may be unrelated to the progression of the disease.

Background

Primary membranous nephropathy (PMN) is now considered an autoimmune-mediated glomerular disease characterized by subepithelial glomerular IgG and complement. The discovery in 2009 of podocyte antigens to which circulating autoantibodies bound brought about a great advance in the basic and clinical research, antibodies against phospholipase A2 receptor (PLA2R) are present in 50 ~ 80% of patients with PMN[1]. However, the pathogenesis of PLA2R-associated MN is obscure. Heymann models of PMN in rats revealed that subepithelial deposits of IgG and C3 resulted from in situ immune deposit formation involving a rat podocyte antigen, and the proteinuria was mediated mainly by complement through the C5b which is a membrane attack complex[2]. Currently, whether complement activation is pathogenic in human PMN or which activation pathway might be involved remain an enigma[3]. IgG4 is the dominant subclass of IgG in PMN, it fails to bind complement and is incapable of activating the classical pathway (CP), studies to date in PMN are consistent with complement is activated through the lectin pathway (LP), and the role of the classical and alternative pathways (AP) has not been completely excluded[4–6]. The complement is intensively activated by IgG1 and IgG3 through the CP in secondary membranous nephropathy (SMN)[7, 8].

Classical pathway activation initiated by C1q which deposits are suggestive of SMN[9]. However, C1q deposition together with IgG and C3 granular deposit is found in many cases of PMN. Currently, the clinical and prognostic significance of C1q deposition in PMN is unclear. In addition, there is a paucity of studies about C1q deposition in children with PMN. Therefore, we conduct this single-center research to define the clinical and prognostic significance of C1q deposition in children with PMN by comparing various clinical and pathological characteristics, treatment response, and long-term renal prognosis in patients with and without C1q deposition.

Methods

1. Participants

All the participants in this study were recruited at Nanjing Jinling Hospital from 2005.07 to 2013.09. The inclusion criteria were: ☐ PMN was histologically proven by kidney biopsy; ☐ age ≤ 18 years; ☐ informed consent was obtained before study commencement. The exclusion criteria were as follows: ☐ patients with secondary causes of MN, including hepatitis B, autoimmune diseases, malignancies, medications, and heavy metal poisoning; ☐ renal pathology presented with “full house” pattern by immunofluorescence, HBc and HBs antigens deposit in glomeruli; ☐ Patients with follow-up less than 12 months in addition to the patient who progressed to end-stage renal disease (ESRD) or related death within 12 months. 73 patients with C1q deposition were enrolled in this study. According to the “Case-control matching principle”, 73 patients without C1q deposition during the same period of the renal biopsy were selected as a control group. Eventually, there are altogether 146 pediatric patients with PMN in this study.

2. Methods

We classified all enrolled patients into 2 groups according to whether C1q deposits in glomeruli. The patient’s general characteristics, clinical and pathological data at biopsy were collected by the reviewing

of medical records. Comparing clinical and pathological characteristics between the patients with and without C1q deposition. The patient's treatment modalities, proteinuria, serum creatinine or eGFR were collected by outpatient and telephone during the follow-up. Comparing treatment responses and long-term renal prognosis in patients with and without glomerular C1q deposits. The baseline was at renal biopsy and all follow-up dates were updated to June 2019.

The primary endpoint was ESRD which defined as $eGFR \leq 15\text{ml}/\text{min}/1.73\text{m}^2$ or the requirement of maintenance dialysis or transplantation. The secondary endpoint was renal dysfunction, defined as eGFR decline by 30% from the time of renal biopsy and to $< 60\text{ ml}/\text{min}/1.73\text{m}^2$. Hypertension was diagnosed according to the criterion recommended by the updating blood pressure references for Chinese children aged 3-17 years established by Jie Mi et al (All enrolled patients were aged 3-17 years). Children less than 16-year-old used Schwartz formula to estimate eGFR, then, eGFR was computed adopting the chronic kidney disease epidemiology collaboration formula (CKD-EPI) among children more than 16 years old. The disease stages were based on Ehrenreich and Churg's classification criteria by electron microscopy. Case-control matching principle was considered that the sex, age, and stage of chronic kidney disease of the case group are matched with the control group. Complete remission (CR) was defined as blood biochemical and urinalysis were completely normal. Partial remission (PR) was defined as proteinuria was qualitatively positive $\leq 2+$ and/ or edema disappeared, a serum albumin level of more than 25g/L. We defined no remission (NR) as proteinuria $\geq 3+$. Relapse was defined as proteinuria of at least 50mg/kg per 24 hours, or urine protein to creatinine ratio (mg/mg) ≥ 2.0 , or proteinuria from negative to 3+ ~ 4+ for 3 consecutive days, except for infections.

Statistical Analysis

The SPSS software (version 19.0, Chicago, IL, USA) was taken for the statistical analysis. Normally distributed variables were presented as the mean \pm SD and compared using Student's t-test. Continuous variables with skewed distributions were expressed as medians and ranges, the nonparametric test was used for comparison. Categorical variables were presented as percentages and compared using the chi-square test. The Kaplan–Meier method was used to calculate renal survival rates and comparisons were by the log-rank test. Risk factors for treatment responses were analyzed using logistic regression analysis. The COX proportional hazard regression model was used to evaluate the relationship between the parameters at baseline and renal survival. All P values were two sides, value < 0.05 was considered statistically significant.

Results

1. Clinical data and renal outcomes of children with PMN.

A total of 146 pediatric patients with PMN included with 86 men (58.9%) and 60 women (41.1%). The median age at onset was 15.0 (14.0–16.0) years. 48 (32.9%) patients presented with hypertension,

nephrotic syndrome occurred in 67.8% of patients.

116 patients (79.5%) received immunosuppressive agents. 126 patients (86.3%) achieved remission, including 83 patients (56.8%) who achieved CR in 8.5[6.4–13.0]months and 43[29.5%]patients who achieved PR in 4.5[3.0–6.0]months. Relapse occurred in 33 patients(22.6%). During an average follow-up of 52.4±35.6 months, 8 patients (5.5%) progressed ESKD, 12 (8.2%)patients developed ESRD or renal dysfunction.

2. Clinical data and renal outcomes of PMN in children with C1q deposition (**Table 1**).

The clinical and pathological features, treatment responses, and renal prognosis of patients with and without C1q deposition were listed in **Table 1**.

73 patients C1q deposition were enrolled in our center, including 43 males (58.9%) and 30 females (41.1%) with a male predominance, the median age at onset was 15.0 (14.0–16.0) years old. 22 patients (30.1%) presented with hypertension and 46 patients (63.0%) manifested as nephrotic syndrome, there were no statistical differences between the two groups ($p_{\text{hypertension}}=0.484$, $p_{\text{nephrotic syndrome}}=0.215$). The frequency of glomerular C4 deposits in the C1q deposits group was significantly higher than no C1q deposits group (34.2% vs 5.5%, $p=0.000$). There were no other distinct differences in baseline characteristics and renal outcomes between the two groups, including proteinuria, serum creatinine, eGFR, the level of serum immunoglobulin and complement, pathological stage, treatment responses, and renal prognosis.

3. The glomerular IgG subclass of PMN in children with C1q deposition (**Table 2**).

Glomerular IgG subclasses were available in 79 patients. There were 37 patients with C1q deposition, 36 (97.3%) with IgG1 deposits, 33 (89.2%) with IgG2 deposits, 30 (81.1%) with IgG3 deposits, 35 (94.6%) with IgG4 deposits. There was no difference in the glomerular IgG distribution between the two groups ($p_{\text{IgG1}}=0.468$, $p_{\text{IgG2}}=1.000$, $p_{\text{IgG3}}=0.988$, $p_{\text{IgG4}}=0.216$).

4. The long-term renal outcomes and related risk factors of PMN in children with C1q deposition.

During an average follow-up of 53.8±35.7 months among the patients with C1q deposition, 3 patients progressed the primary endpoint, the cumulative renal survival rates of the primary endpoint at 5 and 10 years after biopsy were 98.2% and 78.6%, respectively. 4 patients developed the secondary endpoint, the cumulative renal survival rates of secondary endpoint at 5 and 10 years after biopsy were 98.2% and 69.8%, respectively.

The Kaplan-Meier survival analysis was performed to compare the long-term renal survival between the two groups. The results revealed that there was no difference in the renal survival of the primary endpoint ($p=0.415$) (**Figure 1**) and secondary endpoint ($p=0.214$) (**Figure 2**) between the two groups.

Logistic regression analysis was used to explore the risk factors for NR (**Table 3**). The results showed that proteinuria >50mg/kg/day was the only risk factor of NR (OR=1.615, 95% CI=0.609–4.281, p=0.035). However, C1q deposition could not predict NR (p=0.553).

The Cox regression analysis was used to evaluate the relationship between the parameters at baseline and renal dysfunction (**Table 4**). NR was significantly correlated with renal dysfunction in the univariate analysis (HR=8.866, 95% CI = 2.347–33.495, p=0.001). Parameters with P values lower than 0.1 in the univariate were enrolled in the multivariate COX regression analysis. Multivariate Cox regression analysis further confirmed that NR was an independent risk factor of renal dysfunction (HR=9.064, 95% CI = 2.400–34.233, p=0.001). C1q deposition could not predict renal dysfunction (p=0.618).

Discussion

This single-center study was conducted to explore the clinical and pathological characteristics, treatment responses, and renal outcomes of PMN in children with C1q deposition. 73 pediatric patients with C1q deposition were enrolled, 73 patients without C1q deposition were selected according to the Case-control matching principle. Therefore, there was no comparison in age and gender between the two groups. Despite the reported rates were various in children, hypertension seemed to be uncommon in children according to previous reports. There was no significant difference in hypertension between the two groups, but over a third of the patients present with hypertension in both groups. Nephrotic syndrome was the most prominent clinical manifestation in both groups, with no difference in the prevalence, all of which were slightly higher than that in adults with PMN (60%)[3]. The laboratory data consisted of 24-hour urinary protein, serum creatinine, serum albumin, serum IgA, serum IgG, serum IgM, serum C3 of patients in the C1q deposits group were comparable to those in the no C1q deposits group. However, a previous study reported that the level of serum IgG in no C1q deposits group was higher than the C1q deposits group (p=0.008)[10]. Renal pathological parameters included pathological stage, the frequency of glomerular IgA, IgG, IgM deposits were also similar between the two groups. Whereas a retrospective study in adult PMN pointed out that there were less MN stage I patients in the C1q deposits group than no C1q deposits group, and more stage III patients (p<0.001). The positive rates of glomerular IgA (p<0.001), IgM (p=0.011), and C3 (p=0.004) deposits in the C1q deposits group were significantly higher than no C1q deposits group[10]. C4 was activated through the CP or the LP, C4d is a cleavage product of C4 activation. C4d deposition together with C1q and immunoglobulin granular deposit that suggests activation of the classical pathway, C4d with or without immunoglobulin deposition, as well as without C1q deposition, suggested activation of the LP[11,12]. The positive rate of C4 deposits in the C1q deposits group was significantly higher than no C1q deposits group in this cohort. The finding suggests that the CP of complement activation occurs in the C1q deposits group. There was no difference in treatment responses and long-term renal outcomes between the two groups, which consistent with a previous study[10]. The rate of self-recovery in children with PMN is high, the consensus has been reached that immunosuppression should be treated in the presence of nephrotic proteinuria and hypoalbuminemia, proteinuria increased by more than 50% during follow-up, serum creatinine increased by more than 30% during follow-up for 6~12 months, thrombosis and other severe adverse events.

[1,13,14]. However, more than 75 percent of patients were on immunosuppressive agents in both groups. It may be associated with the severity of the patients in our cohort.

C1q deposits generally suggests SMN[2,15], which is a rare finding in PMN (<20%)[16]. None of PMN patients with C1q deposition progressed SMN during follow-up. Therefore, except renal pathology presented with a “full house” pattern by immunofluorescent staining, C1q deposits may not play a pathogenic role in SMN[17,18].

PMN is a rare pathological finding in pediatric patients, occupies 1.5–9% of biopsies during the corresponding period[19]. There is a rarity of data about the prognosis in children with PMN due to small samples with a fairly short follow-up period. Several studies reported that 21–29% of pediatric PMN presented with renal dysfunction at the last follow-up[20]. We performed the Kaplan-Meier survival analysis to compare the long-term renal survival between the patients with and without C1q deposition. The results found that the C1q deposits group showed comparable renal survival compared to no C1q deposits group. According to previous studies, the established risk factors of PMN in adults include age(≥50 years old), gender(male), decreased eGFR on presentation, persistent heavy proteinuria, increased excretion of urinary C3dg, urinary C5b-9 andβ2 microglobulin[3]. Whereas considerably fewer studies have analyzed the association between glomerular C1q deposits and renal outcome. The logistic regression analysis was used to explore the risk factors for NR in this research, and the Cox regression analysis was used to evaluate the relationship between the parameters at baseline and renal survival. As a result, C1q deposition failed to associate with disease progression, which was confirmed by previous studies.

The clinical and pathological characteristics, treatment responses and renal outcomes of patients with C1q deposition were similar to the patients without C1q deposition. These findings show that the CP of complement activation may occur in some patients with PMN, while it has no direct impact on renal injury and may not play an essential role in the pathogenesis of the disease. Thus, the treatment of PMN should target to common pathway rather than any one individual pathway.

Conclusion

The CP does occur in some patients of PMN. However, it may be unrelated to the progression of the disease.

Abbreviations

Primary membranous nephropathy: PMN

Phospholipase A2 receptor: PLA2R

Classical pathway: CP

Lectin pathway: LP

Alternative pathways: AP

Secondary membranous nephropathy: SMN

End-stage renal disease: ESRD

Chronic kidney disease epidemiology collaboration formula: CKD-EPI

Complete remission: CR

Partial remission: PR

No remission: NR

Systemic lupus erythematosus: SLE

Declarations

Ethics approval and consent to participate All data were obtained via electronic medical records and a database review and were de-identified (the patient's name was replaced with an identification code, and the patient's private information was deleted before the analysis) to protect patient privacy. This study was approved by the Institutional Ethics Committee of Nanjing Jinling Hospital ;

Consent to publication: Not applicable;

Availability of data and materials: Not applicable;

Competing interests The authors declare that they have no competing interests;

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Authors' contributions: RW, MQ W both are principal co-investigators, contributed equally to study design, data analysis and draft the manuscript. ZK X, CL G, and ZS are co-investigators who reviewed the data for this study and participated in discussions around the observed outcomes. XF, HY W and YC P are independent members who collected the data. All authors were involved in the writing of the manuscript and the decision to submit the manuscript for publication.

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Tables

Table 1 The parameters of PMN patients with or without C1q deposition.

Parameters	C1q deposit (n=73)	No C1q deposit (n=73)	P
Hypertension, n(%)	22 (30.1)	26 (35.6)	0.481
Nephrotic syndrome, n(%)	46 (63.0)	53 (72.6)	0.215
Hematuria ($\times 10^4$ /mL)	30.00 (5.00—136.00)	17.60 (4.50—93.85)	0.248
Urinary protein (g/day)	2.83 (1.32—4.89)	2.45 (1.34—5.03)	0.809
RBP (mg/L)	0.30 (0.11—0.75)	0.29 (0.11—0.50)	0.691
Urine NAG (U/g*cr)	28.45 (15.65—45.20)	25.70 (15.00—46.40)	0.720
Serum albumin (g/L)	23.69 \pm 6.93	22.54 \pm 5.68	0.968
Cholesterol (mmol/L)	8.45 \pm 2.52	8.48 \pm 3.04	0.953
Triglyceride (mmol/L)	2.15 (1.50—3.10)	2.16 (1.55—3.64)	0.531
Serum creatinine (mg/dl)	0.62 \pm 0.17	0.62 (0.50—0.69)	0.533
eGFR (mL/min/1.73m ²)	148.13 (137.73—175.21)	161.34 (141.07—193.28)	0.154
Serum urea nitrogen(mg/dl)	13.16 \pm 5.07	12.10 (8.91—15.96)	0.490
Serum uric acid (umol/L)	362.97 \pm 98.30	375.14 \pm 108.78	0.432
Serum - IgA (g/L)	1.52 (1.03—2.01)	1.47 \pm 0.60	0.201
Serum - IgG (g/L)	5.18 \pm 2.69	4.41 \pm 2.28	0.053
Serum - IgM (g/L)	1.29 (0.91—1.78)	1.38 (1.03—1.86)	0.329
Serum - C3 (g/L)	1.12 (0.90—1.29)	1.11 (0.97—1.29)	0.670
Serum - C4 (g/L)	0.20 (0.15—0.25)	0.21 \pm 0.06	0.244
Renal pathology, n(%)			
IgA deposit	14 (19.2)	8 (11.0)	0.165
IgM deposit	14 (19.2)	13 (17.8)	0.831
C3 deposit	70 (95.9)	66 (90.4)	0.326
C4 deposit	25 (34.2)	4 (5.5)	0.000
Churg's stages, n(%)			0.522
MN-I	18 (24.7)	16 (21.9)	
MN-II	27 (37.0)	31 (42.5)	
MN-III	26 (35.6)	19 (26.0)	
Immunosuppressive treatments, n(%)	60 (82.2)	56 (76.7)	0.413
Treatment responses, n(%)			
Remission	62 (84.9)	64 (87.7)	0.630
Complete remission	40 (54.8)	43 (58.9)	
Partial remission	22 (30.1)	21 (28.8)	
No remission	11 (15.1)	10 (13.7)	0.814
Relapse, n(%)	13 (17.8)	20 (27.4)	0.166
Renal dysfunction, n(%)	4 (5.5)	8 (11.0)	0.366
ESRD, n(%)	3 (4.1)	5 (6.8)	0.716

RBP: retinol binding protein; NAG:N-acetyl-beta-D glucosaminidase; eGFR: estimate glomerular filtration rate;

Table 2 The glomerular IgG subclass of PMN patients with and without C1q deposits

Glomerular IgG subclass	C1q deposit (n=37)	No C1q deposit (n=42)	P
IgG1	36(97.3%)	42(100.0%)	0.468
IgG2	33(89.2%)	37(88.1%)	1.000
IgG3	30(81.1%)	34(81.0%)	0.988
IgG4	35(94.6%)	42(100.0%)	0.216

Table 3 The logistic regression analysis of the risk factors for no-remission of children with PMN.

Parameter	OR (95%CI)	P
Gender (male)	0.611(0.230—1.620)	0.322
Age (increased by 1 year)	1.019 (0.797—1.301)	0.883
Hypertension	1.656 (0.625—4.385)	0.310
Hypoalbuminemia	3.118 (0.826—11.771)	0.093
Proteinuria > 50mg/kg/day	1.615 (0.609—4.281)	0.035
eGFR	0.998 (0.987—1.008)	0.659
C1q deposition	0.748 (0.287—1.951)	0.553

Table 4 The Cox regression analysis of the risk factors for renal dysfunction in children with PMN

Parameters	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P	HR (95%CI)	P
Gender (male)	6.749 (0.870—52.344)	0.068	5.972 (0.757—47.129)	0.090
Age (increased by 1 year)	1.229 (0.832—1.814)	0.300		
Hypertension	1.309 (0.402—4.261)	0.655		
Hypoalbuminemia	5.971 (0.767—46.486)	0.088	4.381 (0.561—34.194)	0.159
Proteinuria >50mg/kg/day	2.016 (0.646—6.295)	0.227		
C1q deposition	0.428 (0.128—1.431)	0.168		
No remission	8.866 (2.347—33.495)	0.001	9.064 (2.400—34.233)	0.001

Figures

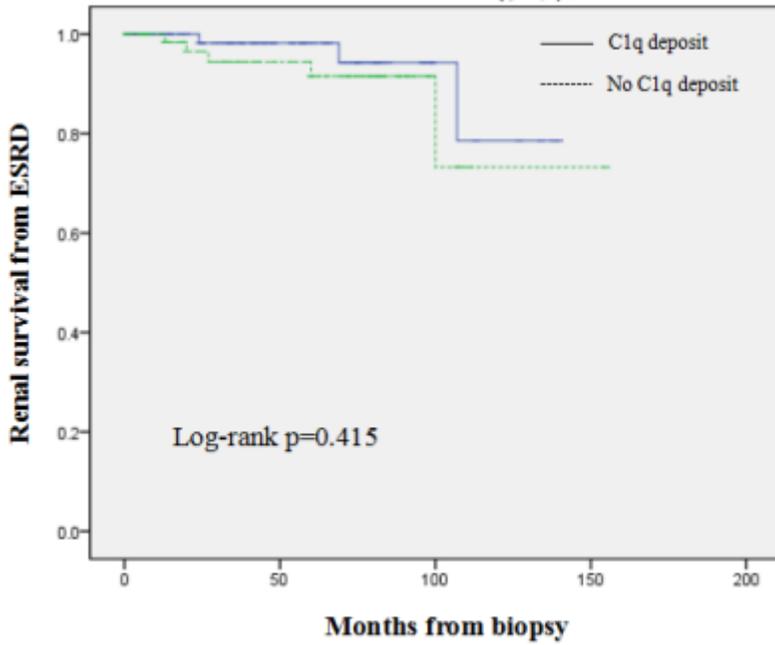


Figure 1

The Kaplan-Meier survival analysis compared the renal survival rates of ESKD between the patients with and without C1q deposition.

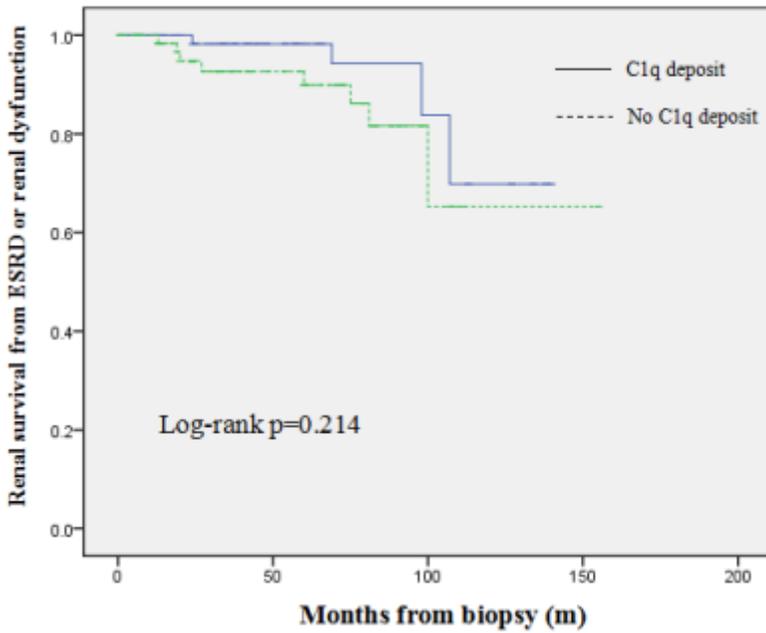


Figure 2

The Kaplan-Meier survival analysis compared the renal survival rates of ESKD or renal dysfunction between the patients with and without C1q deposition