Explanatory histological findings for urinary protein and serum creatinine levels at renal biopsy in lupus nephritis: A cross-sectional study

Eri Katsuyama
Okayama University Graduate School of Medicine Dentistry and Pharmaceutical Sciences
Yoshia Miyawaki
Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
Ken-ei Sada (sadakenn@okayama-u.ac.jp)
Okayama University https://orcid.org/0000-0003-1020-0818
Yosuke Asano
Okayama University
Keigo Hayashi
Okayama University
Yuriko Yamamura
Okayama University
Sumie Hiramatsu-Asano
Okayama University
Michiko Morishita
Okayama University
Keiji Ohashi
Okayama University
Haruki Watanabe
Okayama University
Takayuki Katsuyama
Okayama University
Mariko Narazaki
Okayama University
Yoshinori Matsumoto
Okayama University
Jun Wada
Okayama University

Research article

Keywords: lupus nephritis, active lesions, chronic lesions, urinary protein, serum creatinine

Posted Date: February 6th, 2020

DOI: https://doi.org/10.21203/rs.2.20345/v2

Version of Record: A version of this preprint was published at BMC Nephrology on June 1st, 2020. See the published version at https://doi.org/10.1186/s12882-020-01868-9.

Abstract

Background To evaluate histological active and chronic lesions associated with proteinuria and serum creatinine (SCr) level as common clinical endpoints in many clinical trials for lupus nephritis (LN). Methods One hundred and nineteen patients from 1990 to 2015 with LN class III, IV, and V, as defined by the International Society of Nephrology/Renal Pathology Society classification, were enrolled. Multiple regression analysis was performed to explore semiquantitative histological variables related to urinary protein and SCr levels. Results The mean age of enrolled patients was 45 years and 79% were female. The mean SCr level was 0.87 mg/dl and mean urinary protein was 3.00 g/gCr at the time of the renal biopsy. Class IV (71%) was the most common type, followed by class III (17%) and class V (13%). Multicollinearity was confirmed between monocellular infiltration (variance inflation factor [VIF] = 10.22) and interstitial fibrosis (VIF = 10.29) and between karyorrhexis (VIF = 4.14) and fibrinoid necrosis (VIF = 4.29). After excluding fibrinoid necrosis and monocellular infiltration because of multicollinearity, only urinary protein level was correlated with wire loop (β−coefficient [β]: 1.09 and confidence interval [CI]: 0.35 to 1.83), and SCr level was correlated with glomerular sclerosis (β: 1.08 and CI: 0.43 to 1.74) by multiple regression analysis. Conclusion As urinary protein and SCr levels could not reflect active lesions quantitatively, they might be difficult to be evaluated for response to induction remission treatments in patients with LN.

Background

Although clinical trials for promising therapeutic agents such as B cell targeted therapy, cytokine-targeted therapy (IL-6 and IFN-alpha), and cytotoxic T lymphocyte-associated antigen 4 for lupus nephritis (LN) have been conducted, none have shown improved outcomes in comparison to the control treatments overall [1]. There are several possible reasons, such as the problem of inclusion criteria, study population, sample size, study duration [1, 2], and one study that has focused on the definition of outcome measurements [3, 4].

Proteinuria and serum creatinine (SCr) have been considered promising predictors for renal survival in patients with LN [5-8]; therefore, the primary outcome of most clinical studies for LN is defined by urinary protein and SCr levels [9, 10]. It has previously been shown that chronic lesions in LN, such as chronic index, glomerular sclerosis, and interstitial fibrosis, are related to a poor renal outcome [11, 12]. Estimated glomerular filtration rate (eGFR) is calculated using SCr level, and eGFR and proteinuria are biomarkers for classification of chronic kidney disease [13]. Considering these findings together, proteinuria and SCr level at renal biopsy might just represent chronic lesions as prognostic predictors, but not active lesions which are assumed to be responsive and improvable after immunosuppressive treatment for LN.

The main objective of this study was to explore explanatory histological active and chronic lesions for proteinuria and SCr level in patients with LN.

Methods

Study design, setting, and population

We retrospectively reviewed patients with LN at Okayama University Hospital. Data from 1990-2006 were collected from paper-based records and data from 2007-2015 were collected from electronic-based records. Data collection was completed in 2016-2017. All of the enrolled patients fulfilled the 1997 American College of

Rheumatology revised criteria for the classification of SLE [14]. Patients were eligible for participation in this study if they had a histologically proven diagnosis of LN (class III, IV and V) meeting the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification [15]. Eligible patients were followed up from their first renal biopsy for 10 years until December 2015.

Clinical parameters

The following information was collected at the time of the renal biopsy, before treatment: age, sex, SLE disease activity index 2000, daily maximum dose of prednisone, use of immunosuppressants, SCr and eGFR levels, urinary protein excretion (g/gCr), hematuria (dipstick test >2+, and >5 erythrocytes per high power field), and active urine sediments. The eGFR was evaluated by the equation defined by the Japanese Society of Nephrology [16].

Histological parameters

For all participants, the histological result of the first renal biopsy sample was classified according to the ISN/RPS classification by experienced nephrologists and/or pathologists. Active glomerular lesions were defined by endocapillary hypercellularity, leukocyte infiltration, subendothelial hyaline deposit, interstitial inflammation, karyorrhexis, fibrinoid necrosis, and cellular crescent, and active interstitial lesions were defined by monocellular infiltration. Chronic glomerular lesions were also defined by glomerular sclerosis, fibrosis adhesion, and fibrous crescent, whereas chronic interstitial lesions were defined by interstitial fibrosis. Arteriosclerosis was also defined by chronic lesions. Each renal biopsy sample was processed using light and immunofluorescence microscopy with standard methods of fixation and staining. For semiquantitative analysis, the histological score was calculated as described in our previous study [17], where histological score = (0.5 × number of glomeruli with segmental lesions + 1 × number of glomeruli with global lesions)/total number of glomeruli. Interstitial lesions such as interstitial fibrosis, arteriosclerosis, and monocellular infiltration to interstitial, tubular, and vascular lesions were semi-quantitatively graded on a scale of 0, 1, 2, or 3 (absent, mild, moderate, or severe, respectively). Interstitial lesions were categorized as being at a high or low grade according to a cutoff score of 2.

Outcomes

The primary outcome measures were the urinary protein and SCr levels. The secondary outcome measure was the cumulative renal survival rates from the date of the renal biopsy for 10 years. The renal endpoint was defined as >40% decline in eGFR.

Statistical analysis

Statistical analyses in this study were performed using the Statistical Package of JMP® 14 (SAS Institute Inc., Cary, NC, USA) and STATA v15 (StataCorp, College Station, TX, USA). All statistical tests were 2-sided; p <0 .05

was considered statistically significant in this study. Complete case analysis was performed, excluding patients with missing clinical data at the time of the first biopsy. The descriptive statistics were expressed as mean and standard deviation (SD) for continuous variables and as n (%) for categorical variables. The cumulative renal survival rates were calculated using the Kaplan-Meier analysis. We censored patients that did not reach the renal endpoint when they completed the 10-year follow-up or at the date of the last recorded visit until December 31, 2015, and we calculated the number at risk for reaching the endpoint from the date of the renal biopsy. Survival curves were compared among the patients divided by qualities of urinary protein level and eGFR using log-rank tests.

Subsequently, multiple linear regression (ordinary least squares regression) analysis was performed to explore whether the histological findings contribute to urinary protein and SCr levels. The primary dependent variables were urinary protein and SCr levels at the time of renal biopsy, which were recorded as continuous variables, and the candidate variable was the scored renal histological findings. Urinary protein levels were log-transformed to fulfill the assumption of a normal distribution of the residuals. To address the issue with multicollinearity, which was assessed using variance inflation factor (VIF) [18, 19], we analyzed our data as two separate models excluding highly correlated covariates. As sensitivity analysis, we also performed same multiple linear regression analysis including age and sex.

Results

Patient characteristics at renal biopsy

From a total of 158 patients with LN, 119 patients with ISN/RPS class III, IV, and/or V were enrolled in the present study after eliminating 11 patients with class I, II, or VI; 20 patients with a lack of clinical data; and 8 patients who underwent a re-biopsy. Patient characteristics are shown in Table 1. The mean age was 45 years and 79% were female. The mean SCr level was 0.87 mg/dl and eGFR was 77.3 ml/min/m^2 at the time of the first renal biopsy. Mean urinary protein was 3.00 g/gCr. Forty-six (39%) patients were treated with prednisolone alone and the others were treated with concomitant immunosuppressants for remission induction. For the renal histology, class IV (71%) was the most common type, followed by class III (17%) and class V (13%). The mean (SD) scores of each histological lesion in enrolled patients were as follows: endocapillary proliferation, 0.26 (0.30); karyorrhexis, 0.06 (0.12); fibrinoid necrosis, 0.08 (0.14); rupture of the glomerular basement membranes, 0.01 (0.03); extracapillary proliferation, 0.05 (0.10); wire loop lesion, 0.14 (0.27); hyaline deposits, 0.02 (0.06); membranous, 0.11 (0.28); glomerular sclerosis, 0.11 (0.16); fibrous adhesions, 0.04 (0.07); and fibrous crescents, 0.01 (0.04). The proportions of monocellular infiltration, interstitial fibrosis, and arteriosclerosis with histological grade ≥2 were 43 (36%), 41 (34%), and 23 (19%), respectively. Pearson's correlation coefficient among each histological lesion showed in Supplementary Table 1.

During the mean observation period of 1931 days, 11 (9.2%) patients experienced > 40% decrease in eGFR. There was no significant difference in renal survival rate in 10 years among the patients divided into four categories of urinary protein (Figure (A): log-rank test, $p = 0.37$). The renal survival rate also did not differ among the patients divided by SCr (Figure (B): log-rank test, $p = 0.88$).

Explanatory histological variables for urinary protein levels (log-transformed)

Using all histological variables, we explored explanatory variables related to urinary protein levels by multiple regression analysis (Table 2, Model 1, Mean VIF = 3.08). Wire loop lesion emerged as an independent explanatory variable (β−coefficient [β]: 1.08 and 95% confidence interval [CI]: 0.33 to 1.82). Multicollinearity was confirmed between monocellular infiltration (VIF = 10.22) and interstitial fibrosis (VIF = 10.29) and between karyorrhexis (VIF = 4.14) and fibrinoid necrosis (VIF = 4.29); therefore, we performed multiple regression analysis again after excluding fibrinoid necrosis and monocellular infiltration (Table 2, Model 2, Mean VIF = 1.40). In Model 2, wire loop lesion (β: 1.09 and 95% CI: 0.35 to 1.83) was also detected as an independent explanatory variable for proteinuria. When fibrinoid necrosis and interstitial fibrosis were excluded from the analysis in Model 3, wire loop lesion (β: 1.00 and 95% CI: 0.28 to 1.71) was still detected as an independent explanatory variable (Table 2, Model 3, Mean VIF = 1.40). Sensitivity analysis including age and sex also showed that only wire loop lesion related to proteinuria statistically (β: 1.10 and 95% CI: 0.35 to 1.85 in Model 2; β: 1.01 and 95% CI: 0.29 to 1.73 in Model 3) (Supplementary Table 2).

Explanatory histological variables for serum creatinine levels

As with the exploratory analysis for urinary protein level, we performed multiple regression analysis to explore the explanatory variables related to SCr level using all histological variables (Table 3, Model 1, Mean VIF = 3.08). The following variables emerged as independent explanatory variables: hyaline deposit (β: -1.84 and 95% CI: -3.64 to -0.04) and glomerular sclerosis (β: 1.10 and 95% CI: 0.43 to 1.76) in Model 1. After excluding fibrinoid necrosis and monocellular infiltration in Model 2 and fibrinoid necrosis and interstitial fibrosis in Model 3, glomerular sclerosis was still an independent explanatory variable (Table 3, Mean VIF = 1.40 in Model 2 and Mean VIF = 1.40 in Model 3). As for SCr level, sensitivity analysis including age and sex also showed glomerular sclerosis constantly independent explanatory variable for SCr (β: 1.01 and 95% CI: 0.37 to 1.66 in Model 2; β: 1.01 and 95% CI: 0.38 to 1.64 in Model 3) (Supplementary Table 3).

Discussion

In this study, we explored the explanatory variables in histological findings for urinary protein and SCr levels at renal biopsy. The urinary protein level was reflected only in wire loop, whereas SCr level was only correlated with glomerular sclerosis.

We could not confirm urinary protein and SCr levels as predictive factors for the renal outcome. As several previous reports showed that urinary protein and SCr levels were the main predictors for the renal outcome [5-8], there is no doubt that urinary protein and SCr levels are predictors for renal prognosis. As the patients in the present study had a less severe renal function and a shorter observation period than those in the previous studies, urinary protein and SCr levels might not have been able to predict the renal prognosis in the present study.

Urinary protein level mainly represented the wire loop but not any endocapillary or the extracapillary proliferative lesions in our study. Our previous report showed that only extracapillary proliferation related to poor renal predictors in active lesion [17]. Thus far, the association between histological findings and proteinuria has not been fully elucidated in patients with LN. Some previous reports showed that the urinary protein level was related to activity index [20, 21], while another report showed that proteinuria correlated neither with activity index nor

with chronicity index [22]. Regarding detailed histological findings, one report showed that proteinuria was correlated with the hyaline deposit [12]. Considering these results, it might be difficult to use urinary protein level as a biomarker of treatment response for active LN.

SCr level was the only representative of glomerular sclerosis in our study. This finding is supported by previous studies showing that SCr level mainly reflects chronicity in LN [12, 17, 22] and is correlated with the renal interstitial lesion, sclerotic glomeruli, and tubular atrophy [23, 24]. Although SCr level is a promising biomarker for renal prognosis in patients with LN, it is only related to the chronic lesions; therefore, it is difficult to use SCr level, as well as urinary protein as biomarkers of treatment response for the active lesions of LN.

We recognize limitations of our study. First, this is a cross-sectional study at renal biopsy; therefore, we could not evaluate if urinary protein and SCr levels reflect treatment response of active lesions directly. However, we could conclude that SCr would be difficult to recover to normal range if glomerular sclerosis was found. Second, we could not evaluate treatment effects related to outcomes. Treatment of patients might be adjusted according to not only histological findings but also urinary protein and renal function. Because our patients showed better renal outcome than previous reports [6], we might underestimate the predictive power of proteinuria and renal function for renal outcome.

Conclusions

Urinary protein and SCr levels could not reflect active lesions quantitatively. Therefore, they might not be adequate biomarkers for response to induction remission treatments in patients with LN. Comparing the changes of candidate biomarkers and histological findings before and after treatment would make it possible to establish relevant biomarkers for the treatment response.

Abbreviations

LN, lupus nephritis; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; ISN/RPS, International Society of Nephrology/Renal Pathology Society; SD, standard deviation; VIF, variance inflation factor; β, β − coefficient; and CI, confidence interval.

Declarations

Ethics approval and consent to participate

This study was conducted according to the guidelines of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The study has received approval from the ethics committees of the Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (authorization number: Ken 1905-017), with participants consent implied by an opt-out approach.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

JW has received speaking honoraria from Astellas, Boehringer Ingelheim, Daiichi Novartis, Sankyo, and Tanabe Mitsubishi, and grant support from Astellas, Bayer, Baxter, Chugai, Daiichi Sankyo, Kissei, Kyowa Hakko Kirin, MSD, Novartis, Novo Nordisk, Ono, Otsuka, Pfizer, Teijin, Torii, and Takeda. All other authors declare that they have no competing interests.

Funding

No funding was received for this study.

Authors' contributions

EK, YM, KS, YA, KH, YY, SHA, MM, KO, HW, TK, MN, and YM contributed to the conception and design of the study and the acquisition of data. EK, YM, and KS conducted the analyses. EK, YM, KS, and JW participated in drafting the article and provided intellectual content of critical importance to the work described.

Acknowledgements

The authors thank Tomomi Maruyama for her significant assistance in data management.

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Tables

Table 1. Patient characteristics at renal biopsy

	Total		Missing
	N = 119		(%)
Age, years	45	(±16)	-
Sex, female, n (%)	94	(79)	-
Observed period, day	2958	(±2584)	-
SLEDAI-2K score	16	(±6)	53.8
ISN/RPS classification			
Class III, n (%)	20	(17)	-
Class III+V, n (%)	2	(10)	-
Class IV, n (%)	84	(71)	-
Class IV+V, n (%)	7	(8)	0.8
Class V, n (%)	15	(13)	-
Max dose of PSL, mg/day	37	(±15)	5.0
Immunosuppressive therapy for remission induction			4.2
PSL alone, n (%)	46	(39)	
Cyclophosphamide, n (%)	31	(26)	-
Tacrolimus or ciclosporin, n (%)	22	(19)	-
Mycophenolate mofetil, n (%)	13	(11)	-
Others, n (%)	2	(2)	-
Serum creatinine, mg/dL	0.87	(±0.51)	-
eGFR, ml/min/m^2	77.3	(±31.0)	-
Urinary protein, g/gCr	3.00	(±2.78)	-
Hematuria (scale > 2+), n (%)	52	(44)	2.5
Active urinary sediment, n (%)	77	(65)	4.2

Data are presented as means and the numbers in brackets indicate the standard deviation (SD). SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; ISN/RPS, International S of Nephrology/Renal Pathology Society; PSL, prednisolone; eGFR, estimated glomerular filtration

Table 2. Association of urinary protein levels at renal biopsy (log-transformed) and histological variables in multiple regression analysis

Variables	Model 1		Model 2		Model 3	
	Coeff [95% CI]		Coeff [95% CI]		Coeff [95% CI]	
Active lesions						
Endocapillary proliferation	0.66	[-0.12 to 1.44]	0.64	[-0.13 to 1.41]	0.67	[-0.10 to 1.43]
Karyorrhexis	0.93	[-2.11 to 3.97]	0.87	[-1.14 to 2.87]	0.84	[-1.16 to 2.83]
Fibrinoid necrosis	-0.12	[-2.82 to 2.58]				
Rupture of glomerular basement membranes	2.34	[-5.52 to 10.21]	2.26	[-4.48 to 9.00]	2.14	[-4.60 to 8.87]
Extracapillary proliferation	1.79	[-0.63 to 4.22]	1.77	[-0.62 to 4.16]	1.84	[-0.54 to 4.22]
Wire loop lesion	1.08	[0.33 to 1.82]	1.09	[0.35 to 1.83]	1.00	[0.28 to 1.71]
Hyaline deposits	1.18	[-2.65 to 5.00]	1.12	[-2.65 to 4.89]	1.39	[-2.34 to 5.12]
Membranous	0.64	[-0.07 to 1.35]	0.67	[-0.02 to 1.35]	0.67	[-0.01 to 1.36]
Monocellular infiltration (category)	-0.25	[-1.48 to 0.98]			-0.07	[-0.53 to 0.39]
Chronic lesions						
Glomerular sclerosis	1.13	[-0.28 to 2.54]	1.15	[-0.24 to 2.54]	1.13	[-0.24 to 2.49]
Fibrous adhesion	-0.40	[-3.41 to 2.62]	-0.35	[-3.33 to 2.63]	-0.25	[-3.21 to 2.71]
Fibrous crescents	1.63	[-3.93 to 7.19]	1.60	[-3.76 to 6.95]	1.80	[-3.56 to 7.15]
Interstitial fibrosis (category)	0.23	[-1.01 to 1.47]	0.00	[-0.47 to 0.47]		
Arteriosclerosis (category)	0.15	[-0.38 to 0.68]	0.13	[-0.39 to 0.64]	0.17	[-0.35 to 0.68]

Proteinuria was log-transformed to obtain a better approximation of normal distribution. Covariates; Model 1: all independent explanatory variables; Model 2: explanatory variables excluding fibrinoid necrosis and monocellular infiltration; Model 3: explanatory variables excluding fibrinoid necrosis and interstitial fibrosis. Coeff, β-Coefficient; CI, confidential interval

Table 3. Association of serum creatinine levels at renal biopsy and histological variables in multiple regression analysis

Variables	Model 1		Model 2		Model 3	
	Coeff [95% CI]		Coeff [95% CI]		Coeff [95% CI]	
Active lesions						
Endocapillary proliferation	0.15	[-0.22 to 0.51]	0.16	[-0.20 to 0.52]	0.16	[-0.2 to 0.52]
Karyorrhexis	0.08	[-1.34 to 1.51]	0.20	[-0.74 to 1.15]	0.23	[-0.71 to 1.17]
Fibrinoid necrosis	0.18	[-1.08 to 1.45]				
Rupture of glomerular basement membranes	0.16	[-3.54 to 3.85]	0.34	[-2.83 to 3.52]	0.39	[-2.79 to 3.56]
Extracapillary proliferation	0.37	[-0.77 to 1.51]	0.40	[-0.73 to 1.52]	0.42	[-0.7 to 1.54]
Wire loop lesion	0.13	[-0.22 to 0.48]	0.12	[-0.22 to 0.47]	0.08	[-0.26 to 0.42]
Hyaline deposits	-1.84	[-3.64 to -0.04]	-1.78	[-3.56 to -0.00]	-1.67	[-3.43 to 0.09]
Membranous	-0.17	[-0.50 to 0.17]	-0.19	[-0.51 to 0.13]	-0.15	[-0.48 to 0.17]
Monocellular infiltration (category)	0.22	[-0.36 to 0.80]			0.26	[0.04 to 0.47]
Chronic lesions						
Glomerular sclerosis	1.10	[0.43 to 1.76]	1.08	[0.43 to 1.74]	1.07	[0.43 to 1.72]
Fibrous adhesion	0.73	[-0.69 to 2.14]	0.68	[-0.72 to 2.08]	0.79	[-0.61 to 2.19]
Fibrous crescents	-1.30	[-3.91 to 1.31]	-1.31	[-3.84 to 1.21]	-1.32	[-3.84 to 1.21]
Interstitial fibrosis (category)	0.06	[-0.52 to 0.65]	0.27	[0.05 to 0.49]		
Arteriosclerosis (category)	-0.04	[-0.29 to 0.21]	-0.02	[-0.26 to 0.23]	-0.02	[-0.26 to 0.23]

Covariates; Model 1: all independent explanatory variables; Model 2: explanatory variables excluding fibrinoid necrosis and monocellular infiltration; Model 3: explanatory variables excluding fibrinoid necrosis and interstitial fibrosis. Coeff, β-Coefficient; CI, confidential interval

Figures

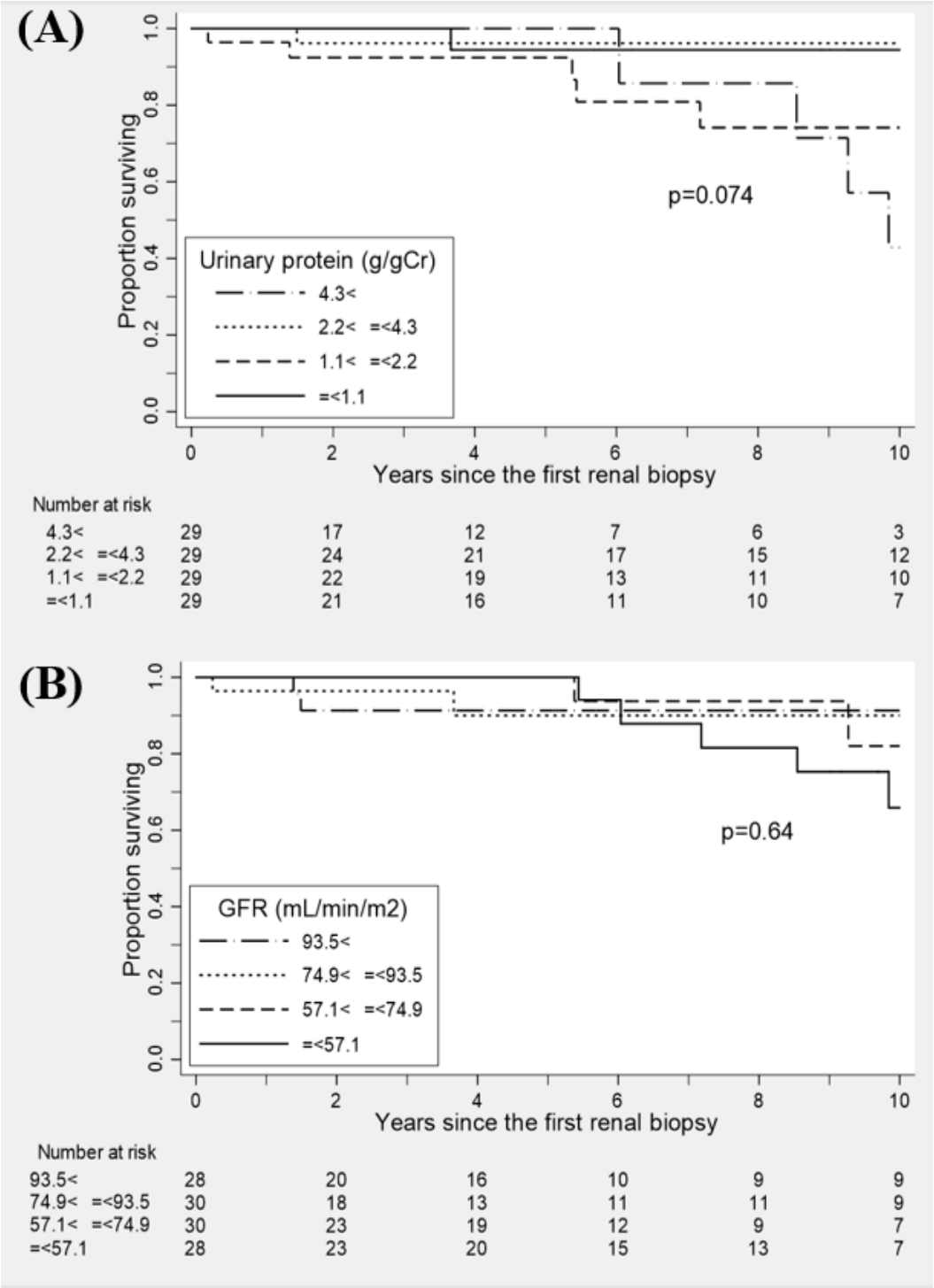

Figure 1

Cumulative renal survival rate of enrolled patients, stratified according to (A) urinary protein levels and (B) estimated glomerular filtration rate (eGFR) at renal biopsy.

Supplementary Files

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- SupplementaryTable.rtf