Proteinuria After 12 Months of Treatment For Lupus Nephritis As Predictor of Long-Term Renal Outcome: A Retrospective Cohort Study

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Abstract

Background: Lupus Nephritis (LN) progression to Chronic Kidney Disease (CKD) and End-Stage-Renal-Disease (ESRD) represents one of the most dreaded complications of Systemic Lupus Erythematosus (SLE), directly impacting quality of life and overall survival in affected patients. Identifying LN patients at high risk for poor renal outcome could lead to individualized management and treatment strategies regarding this population. We hypothesized that 24-hour urine proteinuria (PTU) after 12 months of treatment could act as a predictor of poor renal outcome in LN patients

Methods: two hundred and fourteen patients who were diagnosed with LN and were followed up for more than 10 years in our center were enrolled retrospectively. Receiver operating characteristics curves (ROC) were used to test the best cut-off value of PTU who predict bad long-term renal outcome.

Results: the statistical difference was observed from 12 months when the outcome was ESRD, with a tendency from 6 months (p=0.06). Proteinuria > 0.9g/day at 12 months was the best predictor of ESRD, with the highest AUC (0.72). The sensitivity, specificity, positive predictive value and negative predictive value were 0.83, 0.65, 0.40, and 0.93, respectively. In the first year of LN treatment the serum creatinine was statistically different in any time for CKD (chronic kidney disease), but only at baseline for ESRD.

Conclusions: In a population with more severe LN followed for a long time (>10 years), the cut-off point of PTU > 0.9/day is the best that predict progression to ESRD. The high negative predictive value emphasizes the need for a 1-year PTU-based LN treat to target treatment as a predictor of long-term renal outcome.

Background

Lupus nephritis (LN) occurs in about 50-60% of all patients with systemic lupus erythematosus (SLE) [1-3] and, despite the availability of guidelines and immunosuppressive treatment, kidney disease progresses to end-stage renal disease (ESRD) in 10-25% of such patients.[1,4,5] The identification of short-term prognostic factors predictive of poor long-term outcome in LN would be helpful in clinical practice and in treat-to-target strategies in clinical trials.

Recent studies have identified 24-hour proteinuria (24PTU) as the single-best predictor of long-term renal outcome in lupus nephrits.[6-10]

A prospective cohort study followed 90 patients (most of whom Caucasian) for 7 years (derived from a previous trial) and concluded that PTU <0.7 g/day at 12 months predicted good outcome, with 71% sensitivity and 75% specificity.[8] In the Euro-Lupus Nephritis Trial, PTU <0.8 g/day was found to be the best predictor of good long-term renal outcome, with a sensitivity of 81% and a specificity of 78%.[10]

In Southwestern Brazil, 94 patients were followed for 7 years and confirmed that PTU <0.8 g/day at 12 months as the best predictor of renal outcome (sensitivity 90%, specificity 78%).[9] Despite differences in context (the first two studies were clinical trials while the Brazilian study was conducted in a daily life setting), the cut-off was similar. The inclusion of other variables in the model, such as serum creatinine (sCr)

and hematuria at 12 months, did not improve the performance of PTU as a predictor.[8-10] It is very important to validate PTU as a long-term predictor of renal outcome for different populations, ethnicities, histological classes, immunological profiles and follow-up periods, especially since the parameter is easily quantifiable with inexpensive and non-invasive laboratory methods and has been shown to reliably reflect renal injury.

The purpose of the current study was to evaluate the ability of PTU as a predictor of long-term renal outcome in a large cohort of lupus nephritis patients from Northeastern Brazil.

Methods

Patients

The medical records of 414 patients with SLE previously or currently followed at the Walter Cantídio University Hospital (HUWC/Federal University of Ceará, Fortaleza, Brazil) were reviewed. To be included in the sample, patients had to have been diagnosed with SLE according to the criteria of the American College of Rheumatology,[11] have no associated autoimmune disorders (rheumatoid arthritis, polymyositis, dermatopolymyositis, systemic sclerosis), and have been followed at the HUWC for at least one year or until their death. The prevalence of LN in our cohort of 414 patients was 53.9% (n=233). Nineteen patients were excluded because of incomplete data (n=15), wrong diagnosis (n=1) or overlap with systemic sclerosis (n=3). We retrospectively studied all 214 patients with LN defined as the presence of two consecutive PTU readings >500mg/24 hours and one of the following changes: red blood cell casts or heme-granular casts, or white blood cell casts, or hematuria, or pyuria, in the absence of other causes, and/or an abnormal renal biopsy matching any class in the pathological classification of the World Health Organization/International Society of Nephrology.[12] HUWC is a public university hospital and tertiary-level referral facility. Most users came from socioeconomically underprivileged communities in Fortaleza (the state capital), the hinterland of Ceará, and other states in Northeastern Brazil.

Study parameters

Information was retrieved from the patients' records, including demographic data (gender, race, age at diagnosis of SLE and LN), clinical data (SLE manifestations at any stage, time between LN diagnosis and the first treatment for LN, follow-up time [from diagnosis of LN to the development of chronic kidney disease, ESRD, last evaluation and/or death], induction and maintenance immunosuppressive treatment), immunological data at any time of the disease (antinuclear antibodies, IgG/IgM anticardiolipin antibodies, lupus anticoagulant, anti-dsDNA and anti-Sm antibodies), and laboratory data (serum creatinine, estimated glomerular filtration rate [eGFR] CKD-EPI, serum albumin, and 24PTU).

Chronic kidney disease (CKD) was defined according to the Kidney Disease Improving Global Outcome definition (eGFR <60 mL/min/1.73m^2 for 3 months or longer irrespective of cause. Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens). End-stage renal disease was defined as the need for permanent hemodialysis or peritoneal dialysis. The study protocol was approved by the HUWC Research Ethics Committee and filed under number 90562917.1.3001.5045.

Statistical analysis

All statistical analyses were performed with the software RedCap. The results were expressed as mean values ± standard deviation, or medians and interquartile ranges (IQR) for continuous variables and percentages for categorical variables. The level of statistical significance was set at 5% (p<0.05). Serum creatinine, eGFR and 24PTU were registered at baseline, at 3, 6 and 12 months, at 5 years and/or the last evaluation. Continuous variables were compared using the *t* test or the Mann-Whitney test, while categorical variables were analyzed with the chi-squared test and Fisher's exact test. Receiver operating characteristic (ROC) curves were plotted and the area under the curve was calculated (Youden index) to test the performance of PTU measurements at 6 and 12 months. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were also calculated.

Results

This study enrolled 214 LN patients from a single center. Most patients were female (90.6%) and non-white (54.7%), with a mean age at LN diagnosis of 27.3 ± 9.2 years. Clinical manifestations were mostly musculoskeletal (82.2%), dermatological (73.8%), serositis (46.7%) and lymphopenia (41.5%). The ANA test was positive in 95% (anti-dsDNA 58%, anti-Sm 38.9%, lupus anticoagulant 26.4%, anticardiolipin 15.5%). The mean time between LN diagnosis and first treatment was 1.73 ± 4.8 months. Upon LN diagnosis, the following mean values were registered: sCr 1.45 ± 1.28 mg/dL, urinary protein 2903.9 ± 3051.3 mg/24 hours, serum albumin 2.51 ± 0.78 g/dL, and eGFR 77.5 ± 40.9 mL/min/1.73m^2. Nearly half the patients (47.6%, 102/214) were submitted to renal biopsy. The most prevalent histological LN class was IV (53.9%), followed by III (21.6%). The immunosuppressant most frequently used to induce the first remission of LN was IV cyclophosphamide (55.6%), followed by azathioprine (AZA) (33.5%) and mycophenolate mofetil (MMF) (10.8%). The mean follow-up period of the cohort was 11.2 ± 7.2 years. At the end of follow-up, 93 of 197 patients (47.2%) had CKD, 49 of 191 (25.6%) were on regular dialysis, and 20 patients had died (infections n=5, acute renal failure n=2, rupture of cerebral aneurysm n=1, rupture of aortic aneurysm n=1, bleeding n=3, stroke n=1, other causes n=7).

SLE patients were divided into two groups: those who developed CKD and those who remained with eGFR >60 mL/min/1.73m^2 during follow-up. Patients were also grouped according to whether they developed ESRD, and the parameters PTU and sCr were compared at baseline, 3, 6 and 12 months, at 5 years and/or the last evaluation (Figures 1, 2, 3 and 4). Patients with and without ESRD differed significantly with regard to PTU at 12 months, but a tendency was already descernible at 6 months (p=0.06). In the first year of LN treatment, CKD and non-CKD patients differed significantly with regard to sCr. As for ESRD, sCr levels were only significantly different at baseline.

ROC curves of PTU measurements at 6 and 12 months of follow-up were plotted in order to identify the target that best predicted long-term renal outcome. PTU >0.9 g/day at 12 months was the best predictor (AUC=0.72) of ESRD (Figure 5). Table 1 shows the sensitivity (0.83), specificity (0.65), positive predictive value (0.40) and negative predictive value (0.93) of the model.

Table 1 – Statistical measures of 24-hour proteinuria > 0.9g for end-stage renal disease

Proteinuria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR	NLR
≥900mg/day	83	65	40.8	93.2	2.4	0.25

Table 2 - Characteristics of 24-hour proteinuria studies as a marker for long-term renal outcome in LN

Study	Study Desigh	Sample size	Follow-up (years)	Cut-off (g/day)	outcome	Sensitivity/ specificity (%)	PPV/ NPV (%)	AUC
Tamirou et al.[8]	Trial (MAINTAIN)	90	7	0.7	Good (sCr ≤ 1mg/dL)	71 75	94 29	0.76
Dall`Era et a.l[10]	Trial (Euro-Lupus Nephritis trial)	90	7	0.8	Good (sCr ≤ 1mg/dL)	81 78	88 67	0.83
Ugoline-Lopes et al.[9]	Retrospective cohort	94	7	0.8	Good (sCr < 1.5mg/dL)	90 78	67 94	0.86
Fung et al.[18]	Retrospective cohort	101	7	0.6	Good (sCr ≤ 1mg/dL)	58 83	92 36	0.65
Medeiros et al. (current study)	Retrospective cohort	214	11	0.9	Bad (end-stage renal disease)*	83 65	40 93	0.72

sCr: serum creatinine; PPV: positive predictive value; NPV: negative predictive value; *: ermanent hemodialysis or peritoneal dialysis); AUC: area under curve

Discussion

Several clinical studies have evaluated the ability of short-term prognostic histological factors to predict long-term renal outcome in LN patients, such as elevated sCr at the beginning of LN, hypertension, proteinuria, diffuse proliferative glomerulonephritis, chronic parenchymal injury and tubulointerstitial abnormality.[5,13-16] However, PTU has recently gained prominence as the best predictor of long-term renal outcome in LN.[8,9,10,17]

The current study analyzed 214 LN patients from a single center followed for 11 years on average, 47.2% of whom progressed to CKD and 25.6% to ESRD. Proteinuria >0.9 g/day at 12 months was found to be the best individual predictor of poor long-term renal outcome (ESRD). (sensitivity 83%, specificity 65%, PPV 40%, NPV 93%). Four studies with objectives similar to ours found sensitivity values ranging from 83% to 90%, with cut-off points from 0.6 to 0.8 g/day (Table 2).[8-10,13] Two of these used data from European clinical trials (MAINTAIN and Euro-Lupus), [8,10] while the other two were retrospective analyses.[9,18] Clinical trials are designed for specific treatments and adherence to intervention protocols tends to be much higher than in observational studies; thus, outcomes are likely to be better than in real-life settings. In their cohort of predominantly Caucasian patients, Tamirou *et al.* observed that PTU <0.7 g/day at 12 months was the best predictor of good outcome at 7 years, with 71% sensitivity and 75% specificity,[8] matching the results of the Euro-Lupus trial.[10] Likewise, Dall'Era *et al.* concluded that PTU <0.8 g/day at 12 months maximized sensitivity (81%) and specificity (78%) for good renal outcome.[10] Both studies found that the inclusion of microscopic hematuria at 12 months in the set of outcome criteria significantly decreased sensitivity, whereas the addition of sCr did not improve performance. The Brazilian retrospective cohort study (n=94) mentioned above found a similar cut-off (0.8 g/day) as the best predictor of long-term renal outcome,[9] while the Canadian study found a conspicuously lower cut-off (0.6 g/day), though at the expense of much lower sensitivity (58%) and area under the curve (AUC: 0.65).[17] The authors of the Canadian study pointed out that their cohort had lower baseline 24PTU values than the cohorts of other studies and, in fact, baseline PTU levels were higher in the European studies (Euro-Lupus: 3.0 ± 2.3; MAINTAIN: 3.4 ± 2.9),[8,10] in the Brazilian study (5.4 ± 4.5),[9] and in the present investigation (2.9 ± 3.0) than in the Canadian study (2.3 ± 2.3).[17] Baseline sCr values were also high in the study by Ugolini-Lopes *et al.* (1.73 mg/dL),[9] and in our study (1.45 mg/dL) compared to the values reported in the MAINTAIN study (0.95 mg/dL),[8] the Euro-Lupus study (1.15 mg/dL)[10] and the Canadian study (0.72 mg/dL),[17] indicating more severe nephritis.

An important point to note is that the outcome assessed in our study was end-stage renal disease, defined as the need for permanent hemodialysis or peritoneal dialysis. The studies reviewed above assessed good long-term renal outcome, defined as sCr <1 mg/dL or <1.5 mg/dL. Our findings should, therefore, be interpretated differently; i.e., after 12 months of treatment, PTU >0.9 g/day was predictive of poor renal outcome (ESRD), with 83% sensitivity and 65% specificity. On the other hand, in the MAINTAIN study, for example, PTU <0.7 g/day at 12 months was the best predictor of good renal outcome (sCr ≤1 mg/dL). Thus, a PPV of 40% means that 40% of the patients with PTU >0.9 g/day at 12 months will develop ESRD during the 11-year follow-up period. This is important because it means that 60% of the patients may still experience a good course despite PTU values >0.9 g/day after 1 year of treatment. Patients with PTU <0.9 g/day at 12 months are not likely to develop ESRD because of the high negative predictive value in our

study (93%). Since predictive values depend on the prevalence of the outcome in the population being studied, positive predictive values tend to be higher in referral centers where severe patients are treated.

The sCr values of patients developing CKD were significantly higher at 3, 6, and 12 months and at 5 years and/or the last evaluation than at baseline, suggesting that from baseline onwards serum creatinine is a good predictor of renal outcome. Some studies have shown that the addition to PTU of the variable sCr at 12 months increases specificity, but without improving performance.[8-10,17] In patients progressing to CKD and ESRD, sCr values decrease between baseline and 6 months after treatment, after which they rise again, possibly because the effective treatment of the first months is followed by a decline in immunosuppressants and corticosteroids. In short, the presence of elevated creatinine levels at the beginning of treatment suggests an increased risk of ESRD and the need to optimize immunosuppressive treatment.

Our study may have been limited by the retrospective design and by the real-life setting since LN treatment heterogeneity may have influenced PTU response and outcome. On the other hand, compared to most other studies, our sample was large and follow-up was long, with focus on PTU as a predictor of long-term renal outcome. In addition, our patients came from a single referral center in Northeastern Brazil, with a unique ethnic profile.

Overall, we demonstrated that, in a Brazilian real-life setting, PTU <0.9 g/day at 12 months was the best predictor of long-term renal outcome.

Conclusion

In a population with more severe LN followed for a long period (>10 years), the cut-off point of PTU > 0.9g/day is the best variable for predicting progression to ESRD. The high NPV value emphasizes the need for a 1-year PTU-based LN treat to target treatment as a predictor of long-term renal outcome. Further studies are crucial to define the therapeutic and follow-up approach in this high risk of developing ESRD population.

Abbreviations

24-PTU: 24-hour urine proteinuria

AZA: azathioprine

CKD: Chronic kidney disease

ESRD: end-stage renal disease

LN: lupus nephritis

MMF: mycophenolate mofetil

NPV: negative predictive value

PPV: positive predictive value

ROC: receiver operating characteristics curves

sCr: serum creatine

SLE: systemic lupus erythematosus

Declarations

Ethics approval and consent to participate: The study was in accordance with the ethical standards of the institutional research committee of Universidade Federal do Ceará (IRB approval number 90562917.1.3001.5045) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Consent for publication: Not Applicable

Availability of data and materials: The data that support the findings of this study are available at Hospital Universitário Walter Cantídio, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the correspondent author upon reasonable request and with permission of Hospital Universitário Walter Cantídio.

Competing interest: The authors declare that they have no competing interests.

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Authors' contributions: FNHFB, MMCM and PFCBCF analyzed and interpreted the patient's data regarding lupus nephritis. FNFHFB, LCMB, MXP, MESL, AWSL collected the data. ABVJ was responsible for statistical analysis of the data. FNFHFB, MMCM and PFCBCF were major contributors in writing the manuscript. LCMB, MXP, MESL, AWSL helped in writing and corrections of the manuscript. All authors read and approved the final manuscript.

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Figures

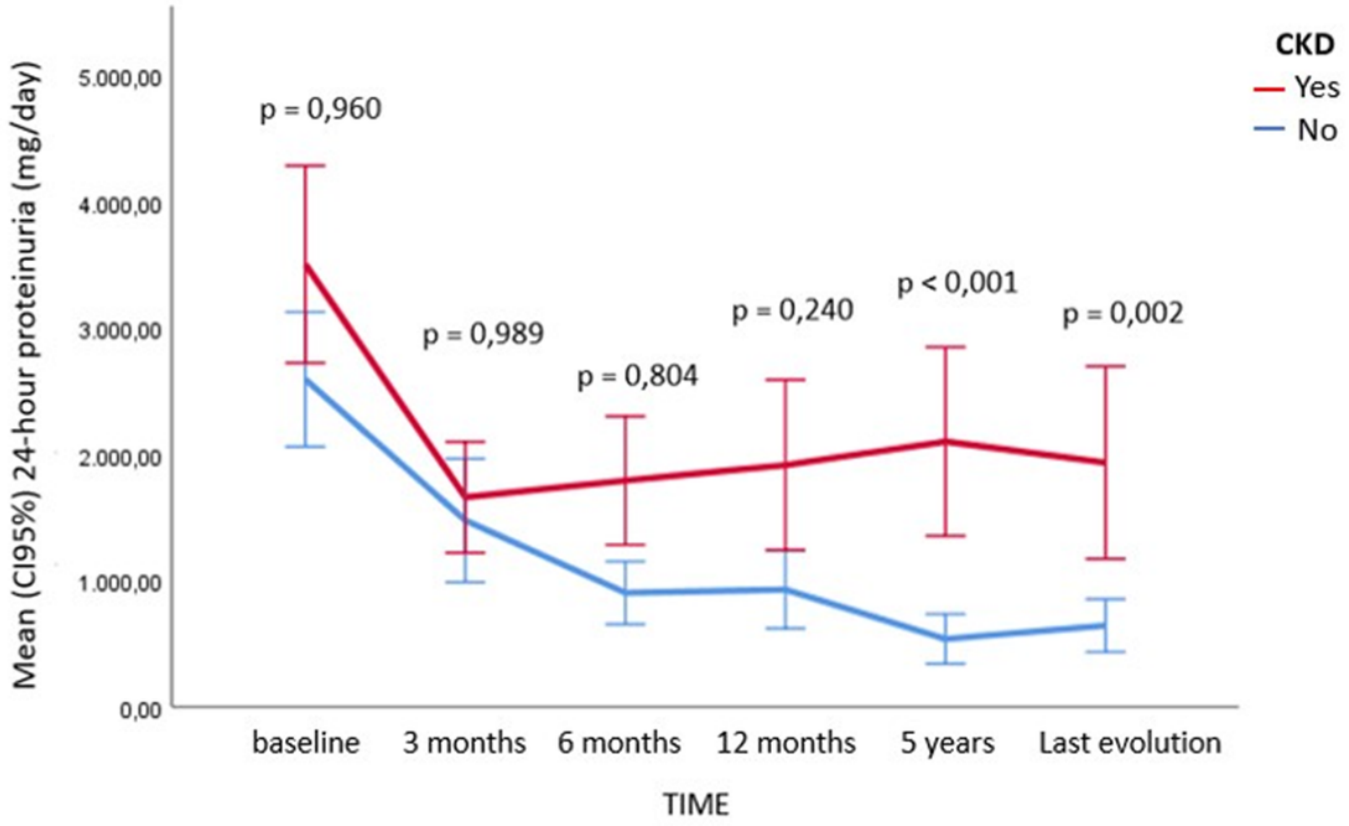

Figure 1

24-hour proteinuria (mg/day) during follow-up in patients with LN who developed CKD and not.

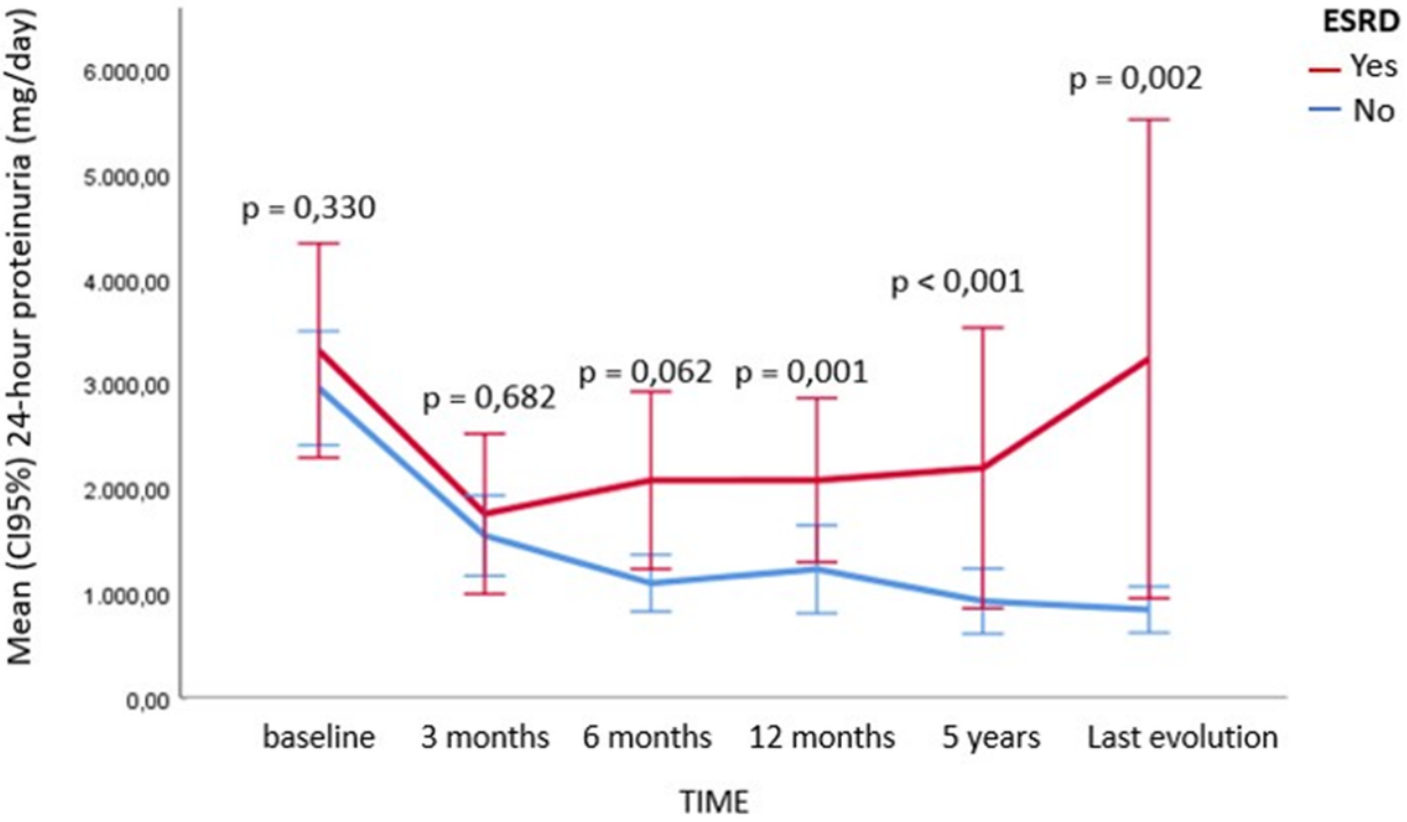

Figure 2

24-hour proteinuria (mg/day) during follow-up in patients with LN who developed ESRD

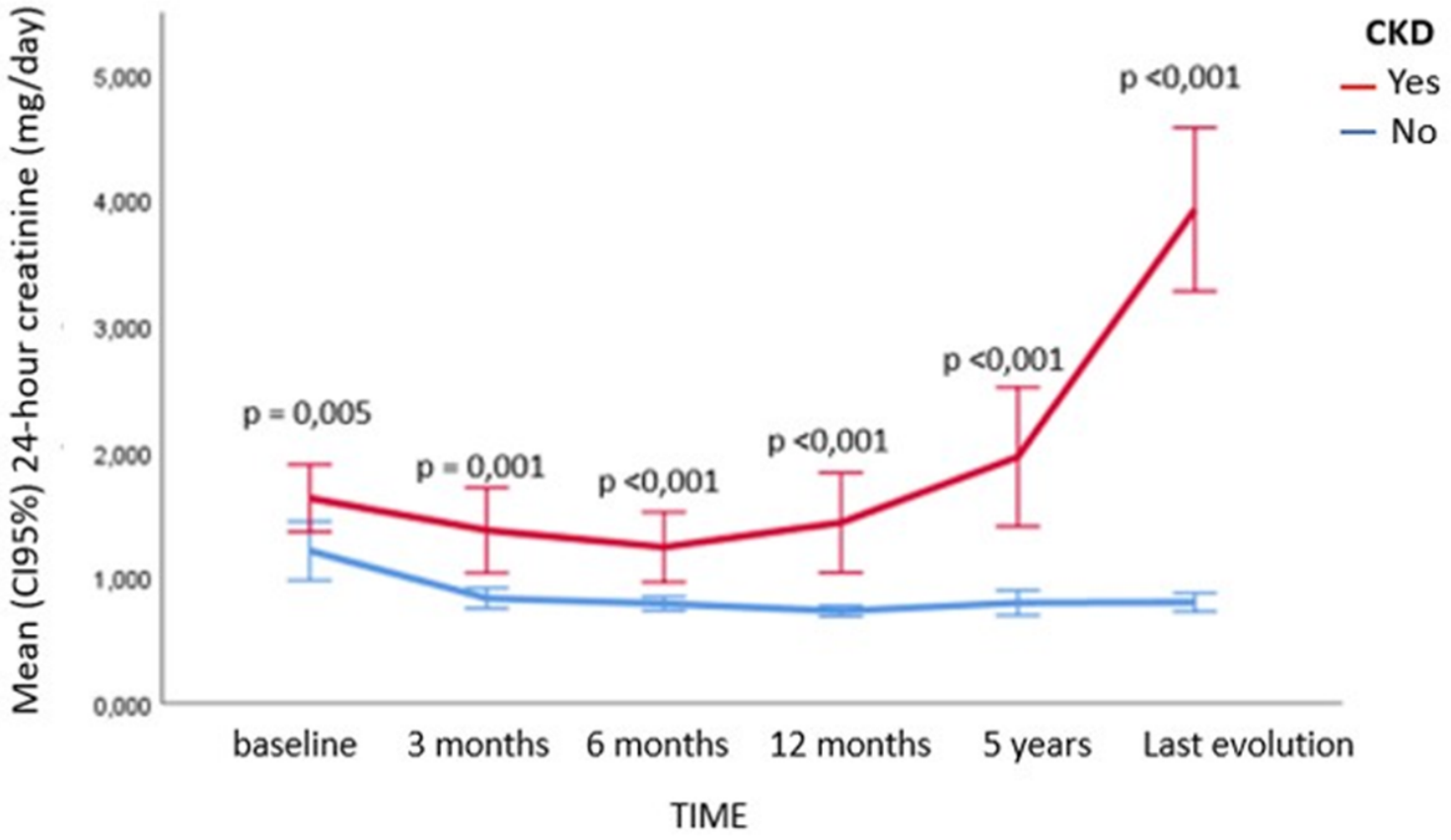

Figure 3

Serum creatinine (mg/dL) during follow-up in patients with lupus who developed CKD and not.

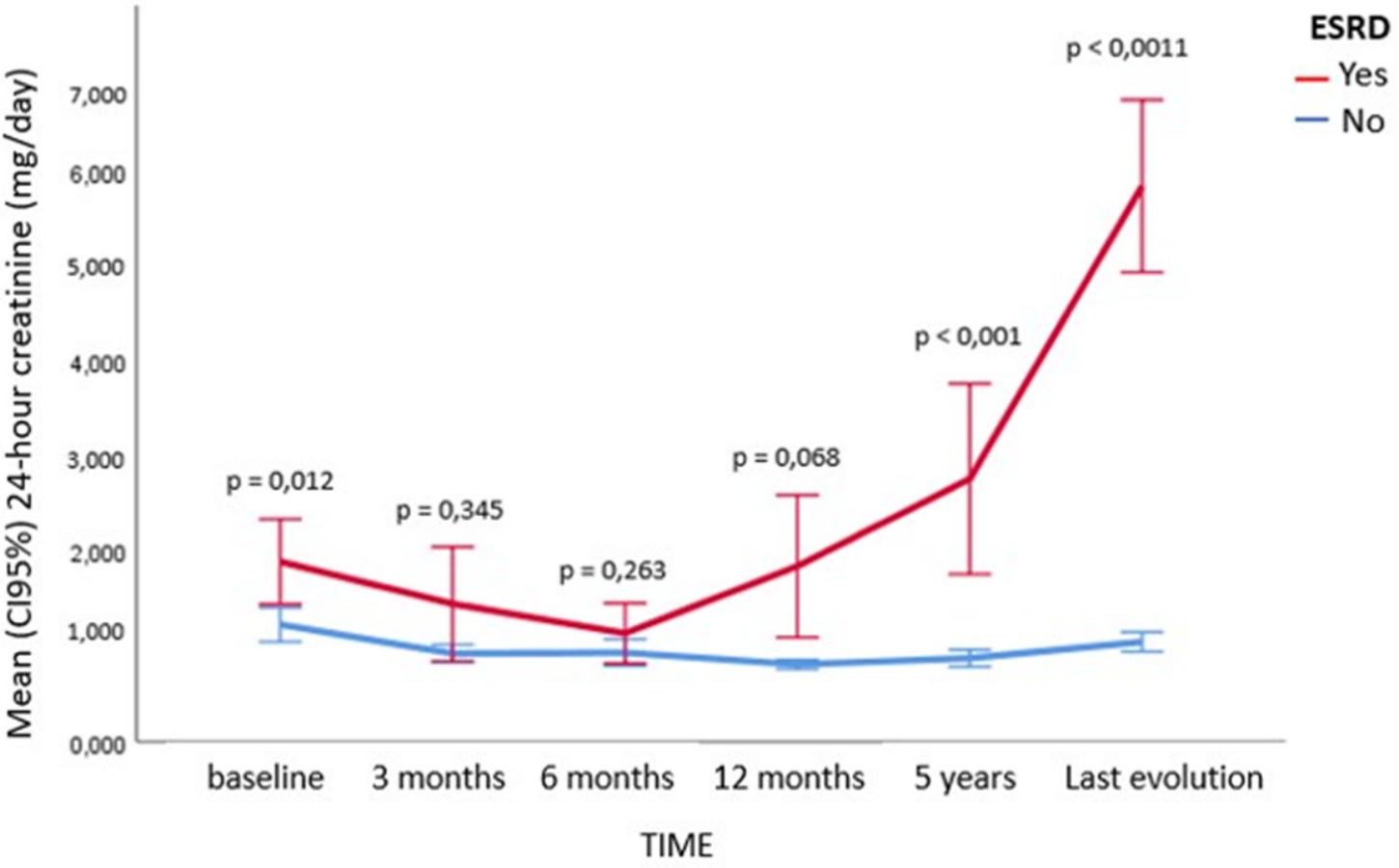

Figure 4

Serum creatinine (mg/dL) during follow-up in patients with lupus who developed ESRD and not.

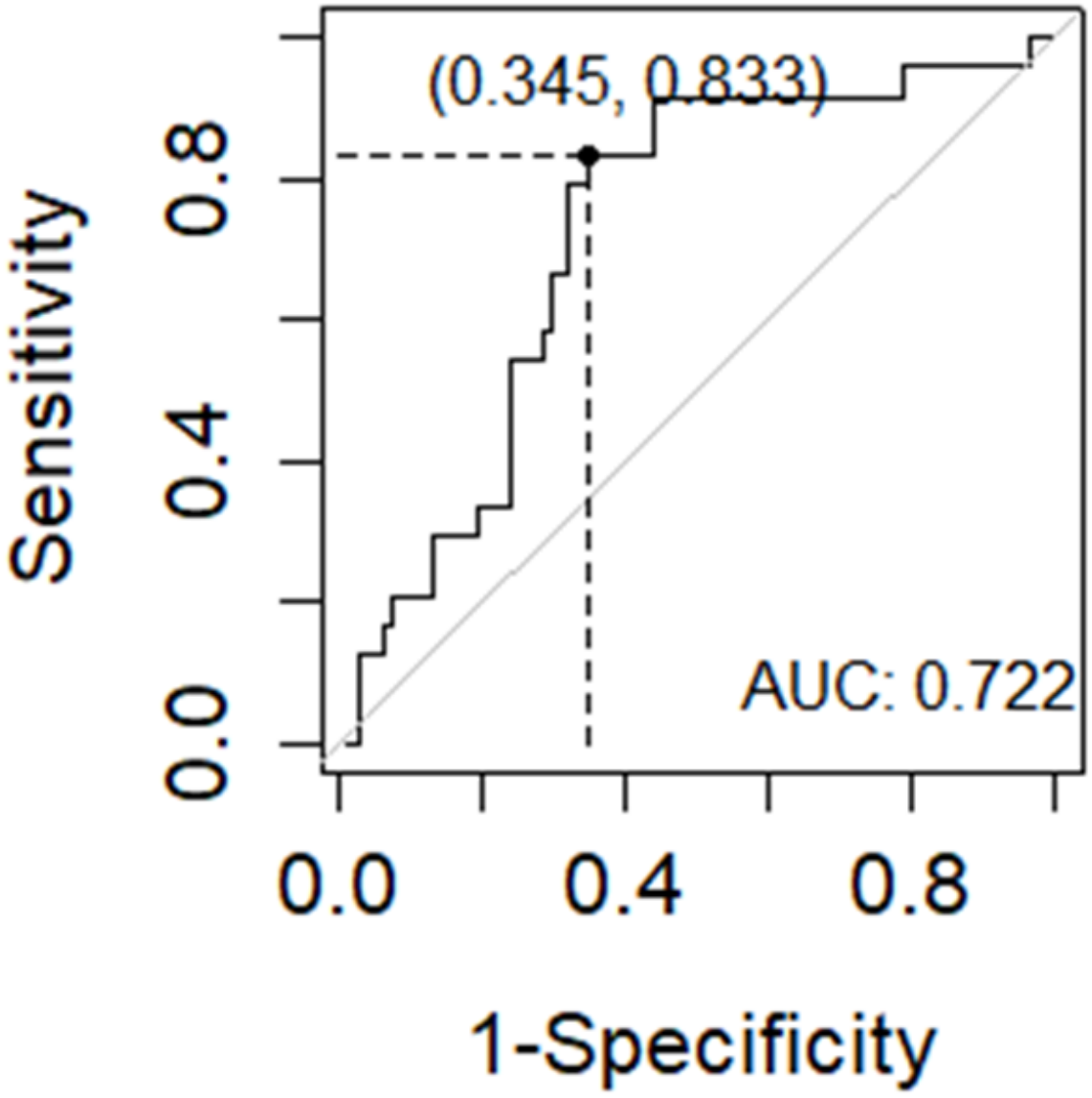

Figure 5

Receiver operating characteristic curve of 24-hour proteinuria at 12 months of follow-up.