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Published in:
Clinical and Experimental Rheumatology

Publication date:
2022

Predictors of renal flares and long-term renal outcome in patients with lupus nephritis: results from daily clinical practice

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Abstract

Objective

To describe renal outcomes of the lupus nephritis (LN) population of the University Medical Centre Groningen (UMCG) in the Netherlands and to identify predictors for renal flares and long-term renal outcome in daily clinical practice.

Methods

A retrospective analysis of biopsy-proven LN patients with induction and maintenance treatment in the UMCG between 1982 and 2016 was performed. Data were collected at time of diagnosis, after 6 months and every year up to 10 years after diagnosis. Outcome measures were renal relapse (biopsy proven), progression to chronic kidney disease (CKD) stage 3 or 4 and chronic renal replacement therapy. The ability of serum creatinine, proteinuria, creatinine clearance, serum anti-double stranded DNA (anti-dsDNA) antibodies, serum complement 3 (C3) and serum complement 4 (C4), as well as biographic data and histopathological class to predict long-term renal outcome was assessed.

Results

Seventy-one patients were included, with median follow-up of 120 months (IQR 48–120 months). During follow-up – up to 10 years – twenty-one (30%) patients experienced at least one relapse. Eleven (15%) patients had CKD stage 3 or 4, of whom eight showed persistent CKD since baseline and two (3%) patients required chronic renal replacement therapy. At baseline, low levels of serum C3 were a significant predictor of renal relapse. Low levels of C3 and C4 at 6 and 12 and proteinuria and high levels of anti-dsDNA at 12 months were significant predictors of renal relapse. At baseline, 6 months and 12 months serum creatinine and creatinine clearance were significant predictors for persistent or newly developed CKD 3 or 4, and need for chronic renal replacement therapy.

Conclusion

Almost one-third of LN patients experience at least one renal relapse during long-term follow up, but only 3% need chronic renal replacement therapy. Our data suggests that early serological remission is associated with a low risk of renal relapse. Decreased renal function at onset and the first year after diagnosis is predictive for decreased renal function at a later stage.

Key words

lupus nephritis, systemic lupus erythematosus, long-term outcome

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Received on September 25, 2020; accepted in revised form on December 14, 2020.

Competing interests: none declared.

Introduction

Lupus nephritis (LN) is a renal manifestation of systemic lupus erythematosus (SLE) and results in significant morbidity and mortality amongst these patients. Although progress in diagnosis and treatment has been made, it is still one of the most common and serious manifestations of SLE, as 50–60% of SLE patients develop LN and 15% of LN patients will develop end-stage renal disease (ESRD) (1-12). In LN, 27% to 66% of all patients experience at least one renal disease flare (13). Renal flares are of great clinical importance, as treatment with additional immunosuppressive medication is necessary, causing extra toxicity. Moreover, the flared disease activity itself causes significant morbidity and added risk on progressive renal failure.

Several predictive factors for renal outcome have already been described in literature, including for example clinical renal remission at 12 months, proteinuria at 12 and 24 months and renal function (increased serum creatinine and decreased creatinine clearance) at baseline (1-12).

The aim of this study is to describe the cohort of LN patients of the University Medical Center Groningen (UMCG) in the Netherlands and to confirm the predictive capabilities of various parameters for a renal flare as well as long-term renal outcome in LN.

Methods

This study was designed as a retrospective cohort study. SLE patients eligible for this analysis fulfilled at least four of the 1982 American College for Rheumatology (ACR) criteria (14). All LN patients diagnosed by renal biopsy at the UMCG between 1982 and 2016 were included. Of these patients, data collected at diagnosis and follow-up visits were recorded and reviewed. These data included laboratory parameters, such as serum creatinine, serum complement 3 (C3), serum complement 4 (C4), serum anti-double stranded DNA (anti-dsDNA) antibodies, proteinuria, estimated glomerular filtration rate (eGFR), leucocyturia and erythrocyturia. Data on induction and maintenance treatment and histopathological class of nephritis (World Health Organisation (WHO) or International Society of Nephrology (ISN) pathological classification) were also recorded. Data were collected at time of diagnosis, 6 and 12 months after diagnosis and every 12 months thereafter up to 120 months after diagnosis, if available. During follow-up, a renal relapse was confirmed by a repeat biopsy.

Concerning histopathological classes, all patients were divided in three groups, namely group 1 (WHO class 1 and 2), group 2 (WHO class 3, 4 and 5 combined with class 3 or 4) and group 3 (WHO class 5 and class 5 combined with class 1 or 2).

Outcome measures were renal relapse, progression to chronic kidney disease stage 3 (eGFR: 30–59 ml/min*1.73m^2) or 4 (eGFR: 15–29 ml/min*1.73m^2) after 12 months of treatment or later on and need for chronic renal replacement therapy (including renal transplantation) during follow up.

Comparable to a recent published article concerning LN, good long-term renal function was defined as serum creatinine level ≤89 μmol/l at seven years follow-up (2). Subsequently, serum creatinine levels of >89 μmol/l at the seven-year follow-up were considered poor long-term renal function.

Statistical methods

Results were expressed as mean ± standard deviation (SD) or median (interquartile range) for normally distributed and non-normally distributed data, respectively. Cox regression analysis was performed to assess the effect of the baseline, 6-month and 12-month parameters on time to renal relapse (biopsy proven) and time to end-point. Generalised estimating equation (GEE) was performed to analyse the course of laboratory parameters over time between patients with and without relapse. Since residuals were non-normally distributed, laboratory parameters were log-transformed before being entered into the models.

p-values less than 0.05 were considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 20 (SPSS, Chicago, IL, USA).

Results

Study entry characteristics

Seventy-one patients were included. The mean age at inclusion was 33.9±13.8 years, 24% were male and disease duration since diagnosis of SLE was one month (interquartile range (IQR) 1–9). All characteristics are shown in Table I. Study entry characteristics were also compared between different groups divided based on histopathological class. As shown in Supplementary Table S1, proteinuria was significantly lower at baseline in group 1 (WHO class 1 and 2) compared to group 2 (WHO class 3, 4 and 5 combined with 3 or 4). Serum C3 levels were significantly lower in both group 1 and group 2 compared to 3 (WHO class 5 and 5 combined with 1 or 2) at baseline.

For 63 of 71 patients, we were able to retrieve data on treatment received. For induction therapy, fifteen patients were treated according to the EUROLUPUS regime (15), which consists of oral prednisone (1 mg/kg/day, max. 80 mg/day) plus intravenous cyclophosphamide (500 mg every two weeks for three months). Nineteen patients were treated with a combination of corticosteroids and high dose cyclophosphamide; 10 patients were treated with corticosteroids and mycophenolate mofetil; 11 patients were treated with a combination of azathioprine and prednisolone; 8 patients received mono-therapy prednisolone.

Table I. Study entry characteristics.

	LN (n=71)
Age (years)	33.9 ± 13.8
Males, n (%)	17 (24%)
Ethnicity	
Caucasian	57 (80%)
Other	14 (20%)
Disease duration (months)	1 (0-9)
Histopathological class	
1 or 2, n (%)	9 (13%)
3, 4, 5+3 or 5+4, n (%)	56 (79%)
5 or 5+1 or 2, n (%)	6 (8%)
Serum creatinine (µmol/ml)	87 (65-170)
Proteinuria (g/24hrs)	2.6 (1.1-5.3)
eGFR (ml/min*1.73m^2)	74 (39-104)
Serum C3 (g/l)	0.53 (0.35-0.74)
Serum C4 (g/l)	0.08 (0.05-0.15)
Serum anti-dsDNA (IU/ml)	195 (32-794)
Leucocyturia	-: 41%, +:41%, ++: 8%, +++: 10%
Erythrocyturia	-: 3%, +: 2%, ++:11%, +++: 84%

Data are presented as mean ± standard deviation or median (interquartile range) for normally distributed and non-normally distributed data, respectively.
LN: lupus nephritis; C3: complement 3; C4: complement 4; anti-dsDNA: anti-double stranded DNA antibodies.

Table II. Patients reaching relapse or study end-point within the 10-year follow-up.

	LN (n=71)
Relapse	
Number of patients with relapse, n (%)	21 (30%)
Number of relapses per patient in relapse group	1 (1-2)
Time to first relapse (months)	36 (24-72)
Renal endpoint	
Total	11 (15%)
Only CKD stage 3 or 4	9 (13%)
Dialysis	1 (1%)
First dialysis, followed by transplantation	1 (1%)

Data are presented as median (interquartile range).
LN: lupus nephritis; CKD: chronic kidney disease.

Renal outcomes

Median follow-up time was 120 months (IQR 48–120 months). Renal outcomes are described in Table II. Of the 71 patients, 21 (30%) had experienced at least one relapse between inclusion and final follow-up visit. Of these patients, 13 experienced one relapse, 4 had two relapses and 4 had three relapses. Median time to the first relapse was 36 months (IQR 24–72).

At baseline, 26 (37%) patients had an eGFR <60 ml/min*1.73m^2. However, within one year renal function of 14 patients (54%) improved to a eGFR of >60 ml/min*1.73m^2. Of the remaining 8 (11%) patients with persistent CKD stage 3 or 4, two patients needed dialysis, of whom one patient is transplanted. An additional three patients develop CKD stage 3 or 4 during the 10-year follow-up, resulting in 11 (15%) patients reaching a renal endpoint. Two additional patients underwent renal transplantation after the 10-year follow-up, at 11 and 29 years after diagnosis, respectively.

Renal relapse

To determine risk factors for renal relapse, we compared patients who did experience a renal relapse (n=21) and those who did not (n=50). As shown in Table III, patients experiencing a renal relapse were significantly younger at diagnosis, and had lower serum C3 levels at baseline. The distribution of the several histopathological classes also differed between both groups as patients with relapse had more often classes 1 or 2. A possible explanation might be the differences in treatment, as in classes 1 and 2 most often no immunosuppressive medication or only prednisolone is given. Indeed, the observed number of relapses seemed to be higher in patients initially treated with corticosteroids alone (6 of the 8 patients (75%)) than in cyclophosphamide (6 of the 34 patients (18%)) or mycophenolate mofetil (1 of the 10 patients (10%)) treated patients. Patients treated with azathioprine tended to have a frequency somewhere in between (5 of the 11 patients - 45%).

To investigate the predictive value of laboratory parameters on time to a renal relapse, Cox regression analysis was performed and hazard ratios (HR)

Table III. Baseline characteristics for patients with and without renal relapse.

	Relapse (n=21)	No relapse (n=50)	*p*-value
Age (years)	27.5 ± 12.5	37.6 ± 13.6	**0.01**
Males, n (%)	5 (24%)	12 (24%)	0.98
Disease duration (months)	2.8 (0.4-12.5)	0.8 (0.1-8.4)	0.34
Follow-up (months)	120 (120-120)	72 (36-120)	**0.01**
Nr. of patients reaching study end-point, n (%)	4 (19%)	7 (14%)	0.59
Histopathological class			
1 or 2, n (%)	6 (29%)	3 (6%)	**0.03**
3, 4, 5+3 or 5+4, n (%)	14 (66%)	43 (84%)	
5 or 5+1 or 2, n (%)	1 (5%)	5 (10%)	
Serum creatinine (µmol/ml)	81 (68-158)	93 (58-184)	0.76
Proteinuria (g/24hrs)	2.8 (0.8-5.3)	2.2 (1.1-5.6)	0.94
eGFR (ml/min*1.73m^2)	82 (46-115)	70 (37-104)	0.37
Serum C3 (g/l)	0.38 (0.29-0.54)	0.61 (0.36-0.79)	**0.04**
Serum C4 (g/l)	0.08 (0.06-0.14)	0.08 (0.04-0.16)	0.99
Serum anti-dsDNA (IU/ml)	451 (15-1000)	177 (35-777)	0.50

Data are presented as mean ± standard deviation or median (interquartile range) for normally distributed and non-normally distributed data, respectively.
CKD: chronic kidney disease; serum C3: serum complement 3; serum C4: serum complement 4; anti-dsDNA: anti-double stranded DNA.

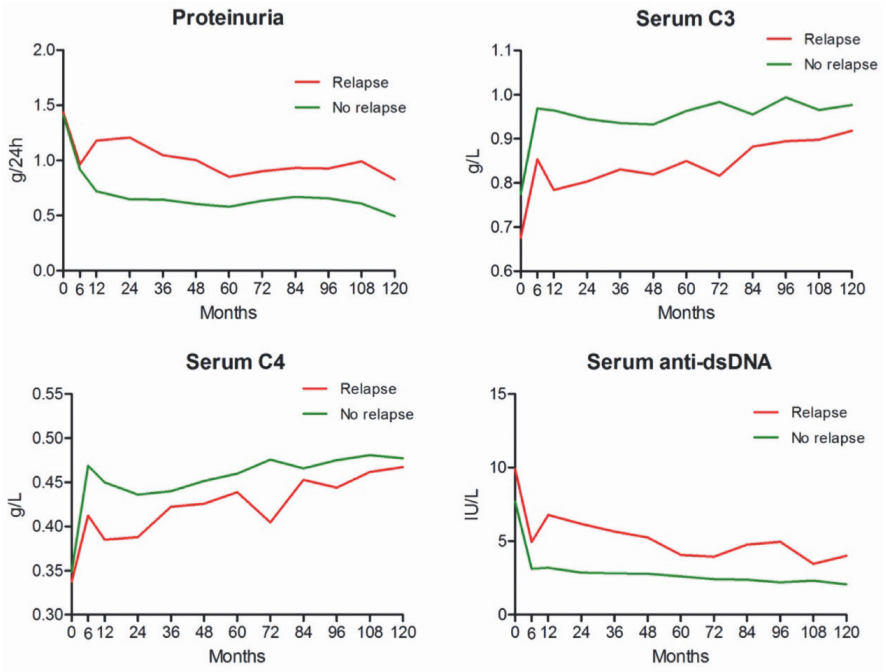

Fig. 1. Course of proteinuria, serum C3, serum C4 and serum anti-dsDNA during follow-up in the groups of patients with relapse and without renal relapse. The courses of all depicted variables differed significantly between both groups based on GEE analysis.

were calculated, which refers to the risk of the occurrence of a relapse (Suppl. Table S2). At baseline, serum levels of C3 was a significant predictor of renal relapse. At 6 months and 12 months of follow-up, serum levels of C3 and C4 were found to be significant predictors of renal relapse. Additionally, at 12 months of follow-up, proteinuria and levels of anti-dsDNA antibodies were significant with time to renal relapse.

To compare the course of the laboratory parameters over time between patients with and without renal relapse, we performed GEE analysis. Of all variables, the course of proteinuria ($p<0.001$), serum C3 ($p<0.001$), serum C4 ($p<0.001$) and serum anti-dsDNA ($p<0.001$) differed significantly between patients who suffered a relapse compared to patients without a relapse within 10 years of follow-up (Fig. 1).

Other renal outcomes, including CKD, dialysis and transplantation

As expected, patients reaching a renal endpoint in this study, had a significant reduced renal function at baseline, with 8 out of 11 showing an eGFR corresponding to CKD stage 3 or 4 at baseline (Table IV). No other significant differences at baseline were present, including the different treatment regimens.

Cox regression analysis showed that serum levels of creatinine and creatinine clearance at baseline, 6 months and after 12 months were significant predictors of other renal outcomes (Suppl. Table S3).

Long-term renal function

Good long-term renal function was defined as serum creatinine ≤89 µmol/ml at 7 years of follow-up, as proposed by Dall'Era *et al*. (2). Data of 42 patients were available at 7 years of follow-up and 23 had serum creatinine levels ≤89 µmol/l and thus were considered to have a good long-term renal function. As shown in Table V, serum creatinine, proteinuria and serum C3 were significantly different at baseline. At the 6- and 12-month follow-up, both serum creatinine and serum C4 were significantly lower and creatinine clearance was significantly higher in patients with good long-term renal function. Proteinuria at 6 months tended to be higher in the patients with poor long-term renal function, albeit not statistically significant.

Discussion

Our study analysed various clinical, histological and biochemical parameters in lupus nephritis (LN) patients, and their effect on the course of the disease and (long-term) renal outcome in daily clinical practice.

By studying the cohort of LN patients, we found that although most patients had WHO or ISN/RPS class 3 or 4 lupus nephritis at diagnosis, only a few patients reached end-stage renal disease and needed renal replacement therapy (3%). In comparison to other studies this is rather low, but it is depending on the definition of outcome in the different studies, the population (for example ethnicity) and the follow up duration (1-12).

Table IV. Study entry characteristics comparing patients with and without renal outcome (chronic kidney disease, dialysis or transplantation)

	End-point (n = 11)	No end-point (n=60)	*p*-value
Age (years)	27.5 ± 19.1	34.4 ± 12.8	0.81
Males, n (%)	1 (9%)	16 (27%)	0.27
Disease duration (months)	0.7 (0.2-24)	0.9 (0.1-8.6)	0.19
Follow-up (months)	108 (36-120)	120 (48-120)	0.76
Patients with a relapse, n (%)	4 (36%)	17 (28%)	0.59
Histopathological class			
1 or 2, n (%)	0 (0%)	9 (15%)	0.18
3, 4, 5+3 or 5+4, n (%)	11 (100%)	45 (75%)	
5 or 5+1 or 2, n (%)	0 (0%)	6 (10%)	
Serum creatinine (μmol/ml)	187 (101-238)	83 (61-154)	**0.01**
Proteinuria (g/24hrs)	2.2 (0.9-3.6)	2.8 (1.1-5.6)	0.58
eGFR (ml/min*1.73m^2)	29 (15-79)	81 (50-109)	**0.01**
Serum C3 (g/l)	0.61 (0.42-0.70)	0.49 (0.31-0.79)	0.50
Serum C4 (g/l)	0.09 (0.06-0.12)	0.08 (0.04-0.15)	0.76
Serum anti-dsDNA (IU/ml)	177 (145-1000)	197 (22-786)	0.58

Data are presented as mean ± standard deviation or median (interquartile range) for normally distributed and non-normally distributed data, respectively.
serum C3: serum complement 3; serum C4: serum complement 4; anti-dsDNA: anti-double stranded DNA.

Table V. Characteristics at entry, at 6 and at 12 months per group divided based on long-term renal function after 7 years

	Good function (n=23)	Poor function (n=19)	*p*-value
Entry characteristics			
Age (years)	29 ± 11.5	34.3 ± 14.5	0.22
Males, n (%)	4 (17.4)	6 (31.6)	0.29
Disease duration (months)	0.8 (0.1-10.3)	1.1 (0.2-7.9)	0.94
Follow-up (months)	120 (48-120)	84 (61-120)	0.35
Histopathological class			
1 or 2, n (%)	6 (26.1)	2 (10.5)	0.40
3, 4, 5+3 or 5+4, n (%)	15 (65.2)	16 (84.2)	
5 or 5+1 or 2, n (%)	2 (8.7)	1 (5.3)	
Serum creatinine (µmol/ml)	81 (60-91)	158 (102-205)	**0.00**
Proteinuria (g/24hrs)	1.6 (0.6-3.1)	4.9 (1.7-7.6)	**0.04**
eGFR (ml/min*1.73m^2)	81 (59-114)	46 (29-99)	0.09
Serum C3 (g/l)	0.45 (0.31-0.7)	0.64 (0.45-0.81)	**0.04**
Serum C4 (g/l)	0.07 (0.06-0.13)	0.12 (0.08-0.18)	0.10
Serum anti-dsDNA (IU/ml)	187 (34-1000)	177 (33-766)	0.89
Characteristics at 6 months			
Serum creatinine (µmol/ml)	79 (69-85)	125 (86-145)	**0.00**
Proteinuria (g/24hrs)	0.3 (0.1-1.5)	1.1 (0.5-2.5)	0.07
eGFR (ml/min*1.73m^2)	102 (87-118)	68 (44-103)	**0.03**
Serum C3 (g/l)	0.87 (0.66-1.10)	0.94 (0.7-1.09)	0.33
Serum C4 (g/l)	0.14 (0.11-0.18)	0.23 (0.16-0.30)	**0.01**
Serum anti-dsDNA (IU/ml)	12 (8-53)	18 (3-59)	0.61
Characteristics at 12 months			
Serum creatinine (µmol/ml)	78 (72-86)	98 (85-130)	0.00
Proteinuria (g/24hrs)	0.6 (0.2-1.8)	0.9 (0-2.9)	0.90
eGFR (ml/min*1.73m^2)	98 (74-132)	72 (43-104)	**0.02**
Serum C3 (g/l)	0.84 (0.63-1.04)	1 (0.58-1.13)	0.40
Serum C4 (g/l)	0.11 (0.09-0.14)	0.21 (0.15-0.26)	**0.00**
Serum anti-dsDNA (IU/ml)	21 (4-122)	10 (6-53)	0.94

Data are presented as mean ± standard deviation or median (interquartile range) for normally distributed and non-normally distributed data, respectively.
serum C3: serum complement 3; serum C4: serum complement 4; anti-dsDNA: anti-double stranded DNA.

We also demonstrated that 30% of our patients suffered at least one renal relapse within 10 years of follow-up. A comparable relapse rate was found in the Rheumatology Registry of Patients with Systemic Lupus Erythematosus (RELESSER) study (5). However, other studies reported a renal relapse rate between 37% to 81% (3, 6-10). This difference could, at least in part, be explained by the fact in the current study renal relapse had to be confirmed by renal biopsy, whereas in other studies this was not necessary. Furthermore, the time period when a study is performed influences the rates of renal relapses and also renal endpoints, as the use of hydroxychloroquine and ACE-inhibitors are more and more common nowadays, which might influence the renal outcomes. In our study, only 24 (34%) patients used hydroxychloroquine and 30 (42%) ACE inhibitors, which is in the current practice more often prescribed. So probably, when this retrospective database analysis is repeated at this moment an even lower relapse rate and incidence of renal endpoint might be expected.

By comparing patients with and without a renal relapse, we showed proteinuria, serum C3, serum C4 and serum anti-dsDNA had a significantly different course during total follow-up in these two groups. In the relapse group proteinuria and serum anti-dsDNA were increased, and serum C3 and C4 were decreased. Furthermore, at early follow-up (6 and 12 months), we found increased proteinuria, increased levels of anti-dsDNA and decreased levels of serum C3 and C4 to be predictors of renal relapse. These results show an association between achieving remission of serological disease activity and less relapses in the future. For SLE in general, studies have shown moderate treatment of serological active disease could prevent disease exacerbations (16, 17) Yap *et al*. reported that indeed pre-emptive treatment at asymptomatic serologic activity leads to an increased renal flare-free survival (18). However, the disadvantage of this approach is more side-effects of treatment and also unnecessary treatment for a part of the patients. Regarding the relapse rate and the different treatments modalities, our data suggests that treatment of LN with cyclophosphamide or mycophenolate mofetil is superior in preventing relapses compared to azathioprine and prednisolone mono-therapy.

Furthermore, the current study demonstrated that decreased renal function

(increased serum creatinine and decreased creatinine clearance) at baseline is a predictor of decreased renal function during follow-up, which is in agreement with what is found by other investigators (5, 10). We also showed decreased renal function at baseline, at 6 and at 12 months follow-up is a predictor of poor renal function during further follow-up. Earlier studies showed amount of proteinuria at 12 months (11) and 24 months (4) tended to predict renal outcome (*e.g.* CKD, ESRD), but the current study did not confirm these results. This might have been due to the small sample-size and low prevalence of these study endpoints.

Lastly, when comparing patients with good and poor renal outcome at 7 years follow-up, in the good outcome subgroup better renal function at inclusion and the first year of follow-up was found, reflected by lower serum creatinine, increased creatinine clearance and lower proteinuria, comparable to earlier studies (2, 11). Interestingly, serum levels of C3 (at baseline) and C4 (at 6- and 12-month follow-up) were significantly higher in patients with poor renal outcome. However, in both renal outcome groups, levels of C4 were above normal range, and therefore these findings probably are of little clinical relevance. However, levels of serum C3 did differ at baseline. As serum levels of C3 are associated with SLE disease activity, it might be expected that lower complement levels at baseline would lead to worse renal function at 7 years of follow-up, as disease activity can cause renal damage. However, this study found opposite results. It can be hypothesised those patients with lower C3 levels at baseline had more inflammation, hence more disease activity, and thus responded better to immunosuppressive treatment, then patients with already more damage instead of inflammation.

This study had some limitations. Despite this study was performed in a tertiary expertise centre for SLE, it remains a retrospective, single-centre design study with and a relatively small sample-size. Since the number of events was relatively low, the power of this study was not sufficient to correct univariate analyses for multiple comparisons. However, the difference in proteinuria, serum C3, serum C4 and serum anti-dsDNA between patients with and without renal relapse was confirmed by the GEE analysis over time. Furthermore, the findings regarding serum creatinine and creatinine clearance as predictors for other end-points were consistent in the different models, indicating the robustness of these results. Also, repeat biopsy and intensified treatment were used to detect renal relapse, and thus only captured the more severe disease exacerbations.

In conclusion, our study using data from daily clinical practice showed although 30% of our patients experience at least one renal disease exacerbation within 10 years, there is little chance on reaching ESRD. Furthermore, these data suggest that early achievement of serological remission might prevent relapse. We also showed decreased renal function at onset is predictive for decreased renal function at a later stage.

References

1. MEJIA-VILET JM, CORDOVA-SANCHEZ BM, ARREOLA-GUERRA JM, MORALES-BUENROSTRO LE, URIBE-URIBE NO, CORREA-ROTTER R: Renal flare prediction and prognosis in lupus nephritis Hispanic patients. *Lupus* 2016; 25: 315-24.
2. DALL'ERA M, CISTERNAS MG, SMILEK DE *et al*.: Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol* 2015; 67: 1305-13.
3. MAHMOUD GA, ZAYED HS, GHONIEM SA: Renal outcomes among Egyptian lupus nephritis patients: a retrospective analysis of 135 cases from a single centre. *Lupus* 2015; 24: 331-8.
4. MEDINA-ROSAS J, FUNG W, SU J, TOUMA Z: Effect of complete or partial proteinuria recovery on long-term outcomes of lupus nephritis. *Semin Arthritis Rheum* 2018; 47: 557-64.
5. GALINDO-IZQUIERDO M, RODRIGUEZ-ALMARAZ E, PEGO-REIGOSA JM *et al*.: Characterization of patients with lupus nephritis included in a large cohort from the Spanish Society of Rheumatology Registry of Patients with Systemic Lupus Erythematosus (RELESSER). *Medicine* (Baltimore) 2016; 95: e2891.
6. MOMTAZ M, FAYED A, WADIE M *et al*.: Retrospective analysis of nephritis response and renal outcome in a cohort of 928 Egyptian lupus nephritis patients: a university hospital experience. *Lupus* 2017; 26: 1564-70.
7. PAKCHOTANON R, GLADMAN DD, SU J, UROWITZ MB: Sustained complete renal remission is a predictor of reduced mortality, chronic kidney disease and end-stage renal disease in lupus nephritis. *Lupus* 2018; 27: 468-74.
8. RIJNINK EC, TENG YKO, WILHELMUS S *et al*.: Clinical and histopathologic characteristics associated with renal outcomes in lupus nephritis. *Clin J Am Soc Nephrol* 2017; 12: 734-43.
9. LIM CC, TAN HZ, HAO Y *et al*.: Long-term renal outcomes in multi-ethnic Southeast Asians with lupus nephritis: a retrospective cohort study. *Intern Med J* 2018; 48: 1117-23.
10. AYODELE OE, OKPECHI IG, SWANEPOEL CR: Predictors of poor renal outcome in patients with biopsy-proven lupus nephritis. *Nephrology* (Carlton) 2010; 15: 482-90.
11. FUNG WA, SU J, TOUMA Z: Predictors of good long-term renal outcomes in lupus nephritis: results from a single lupus cohort. *Biomed Res Int* 2017; 2017: 5312960.
12. SIGNORINI V, ELEFANTE E, ZUCCHI D, TRENTIN F, BORTOLUZZI A, TANI C: One year in review 2020: systemic lupus erythematosus. *Clin Exp Rheumatol* 2020; 38: 592-601.
13. SIDIROPOULOS PI, KRITIKOS HD, BOUMPAS DT: Lupus nephritis flares. *Lupus* 2005; 14: 49-52.
14. TAN EM, COHEN AS, FRIES JF *et al*.: The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271-7.
15. HOUSSIAU FA, VASCONCELOS C, D'CRUZ D *et al*.: Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002; 46: 2121-31.
16. BOOTSMA H, SPRONK P, DERKSEN R *et al*.: Prevention of relapses in systemic lupus erythematosus. *Lancet* 1995; 345: 1595-9.
17. TSENG CE, BUYON JP, KIM M *et al*.: The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; 54: 3623-32.
18. YAP DY, KWAN LP, MA MK, MOK MM, CHAN GC, CHAN TM: Preemptive immunosuppressive treatment for asymptomatic serological reactivation may reduce renal flares in patients with lupus nephritis: a cohort study. *Nephrol Dial Transplant* 2019; 34: 467-73.