Clinical Characteristics and Prognosis of Renal Thrombotic Microangiopathy in Lupus Nephritis

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Introduction. LN is an important complication affecting the prognosis of SLE. We retrospectively analysed the influence of thrombotic microangiopathy (TMA) on LN, identified risk factors of TMA in LN and renal failure in LN-TMA, and evaluated the availability of plasmapheresis.

Methods. After balancing epidemiological characteristics and pathological types between groups, 127 patients (LN-TMA:42, LN:85) were included. After consulting medical records and follow-up data, we used the corresponding statistical methods, such as chi-squared test and Student's t-test, to compare differences in various aspects and explore the correlation among factors.

Results. LN-TMA patients had significantly higher blood urea nitrogen (13.2 mmol/L vs. 7.5 mmol/L, $P < .001$), systolic and diastolic blood pressures (both $P < .01$), serum creatinine (157.75 µmol/L vs. 79.00 µmol/L, $P < .001$), lactic dehydrogenase ($P < .05$), renal activity index (8.00 vs. 2.00; $P < .001$), SLE disease activity index score (13.8 ± 3.4 vs. 10.88 ± 6.0; $P < .01$), and pleurisy ($P < .01$) and lower haemoglobin (84.4 ± 20.14 vs. 99.38 ± 23.45 g/L, $P < .05$), platelets (87 vs. 155 $\times 10^9$/L, $P < .001$), estimated glomerular filtration rate (39.24 vs. 97.40 mL/min/ 1.73m^2, $P < .05$), and 3- and 5-year renal survival rates ($P < .001$ and $P < .01$, respectively) than non-TMA patients. Infection and TMA ($P < 0.01$) were independent risk factors for LN-TMA and renal failure, respectively. There was no obvious effect of plasmapheresis.

Conclusion. TMA is an independent risk factor for renal failure in LN. As TMA affects the severity and prognosis of LN, identifying specific diagnostic indicators and effective treatment for LN is necessary.

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INTRODUCTION

As a serious complication of systemic lupus erythematosus (SLE), lupus nephritis (LN) is involved in immune dysfunction and inflammation. It is commonly observed in 40% of SLE[1] cases and is the primary cause of death among patients with SLE.[2] Although glucocorticoid with immunosuppressive therapy has decreased the mortality rate, there are still some patients who have no obvious effect on it.[3] 5 to 20% of patients with LN progress to chronic kidney disease (CKD) within 10 years.[4] So far, studies have mostly focused on glomerular lesions and have paid less attention to vascular lesions. However, it has been found that the incidence of vascular lesions is as high as 81.8% in LN.[5] Vascular lesions includes five types:

1) arteriosclerosis, 2) vascular immune complex deposits, 3) thrombotic microangiopathy (TMA), 4) true renal vasculitis, and 5) non-inflammatory necrotising vasculopathy.[6] Emerging evidence has shown that vascular lesions are associated with the poor prognosis of LN.[7] Among them, patients with TMA have the worst outcome despite accounting for only 17.6% of cases of LN.[8,9] TMA is a pathology that results in vascular lesions caused by vascular endothelial injury. It is characterised by diverse symptoms including thrombocytopenia, microvascular haemolytic anaemia, and renal failure.

Because of the low incidence of TMA, descriptive previous studies were performed mostly. Thus, the prognosis of TMA and its influence on LN are speculative. The aim of this retrospective study was to characterise the clinical and pathological features of LN-TMA and to further explore whether TMA influences the prognosis of LN. Additionally, we also investigated the risk factors of renal failure and death in LN-TMA to facilitate early intervention. Evaluating the effectiveness of plasmapheresis may be a better guide to aetiology and treatment.

MATERIALS AND METHODS

Patients

Patients with LN admitted in the First Affiliated Hospital of Zhengzhou University from August 2013 to January 2019 were included in our study. The inclusion criterion was a renal biopsy-confirmed LN diagnosis. This study was conducted following the Helsinki Declaration of 1964 and its revised ethical standards and was approved by the Ethics Committee of our hospital; the verbal consent of each patient was acquired. Patients with hepatitis or cancer, those who were pregnant, and those with other connective tissue diseases were excluded.

Clinical Indicators

Patients were divided into LN-TMA group and non-TMA group according to the availability of TMA; the non-TMA group was matched with the LN-TMA group by sex, age, and pathological type. The following variables were collected from both groups: 1) General Information: sex, age, disease course, systolic and diastolic blood pressure, complete blood count, urinalysis, liver and kidney function tests, blood lipids, electrolytes, thyroid function tests, lactic dehydrogenase (LDH), and the number of patients requiring dialysis during renal biopsy; 2) LN-specific Indicators: clinical manifestations, C-reactive protein levels, erythrocyte sedimentation rate, level of autoantibodies and complements, and SLE disease activity index (SLEDAI) score; and; 3) Kidney Pathological Indicators: renal pathological type, renal activity index (AI), and renal chronic index (CI). All these data were collected from medical records.

Follow-Up and Prognosis

The starting point of follow-up was the time of renal biopsy, and was concluded when the last follow-up or endpoint event occurred, which was defined as all-cause death or renal failure (estimated glomerular filtration rate [eGFR] < 15 ml/min). Urinalysis and 24-hour urine protein quantification, serum creatinine (sCr), and serum albumin levels were obtained at 6 and 12 months after treatment. The partial remission (PR) rates, complete remission (CR) rates, and 3- and 5-year renal survival and overall survival rates were compared between the two groups. Patients undergoing plasmapheresis during the follow-up were selected for analyses of the relevant clinical data before, after, and 2 months after treatment to analyse the efficacy of the procedure. The baseline clinical data of patients with renal failure during the follow-up were collected, and risk factors for renal failure were analysed.

Definitions

As diagnostic criteria, we used the SLE classification criteria that were revised by the American College of Rheumatology in 1997.[10] The disease activity score was based on the SLEDAI score sheet.[11] The pathological classification criteria were based on ISN/RPS, 2003.[12] The renal tissue AI and CI were based on the NIH scoring criteria.[13] The pathological diagnostic criteria of thrombotic microvascular lesions were defined as endothelial cell swelling on light microscopy, lumen stenosis or occlusion, interlobular thrombosis and glomerular capillary injury, inner loose layer widening, and endothelial cell swelling under an electron microscope.[14] Renal TMA was defined as lesions of interlobular arteries, arterioles, and glomerular capillaries, including lumen narrowing or occlusion, endothelial cell swelling, and thrombosis observed under light microscopy. Meanwhile, electron

microscopic observation showed that the glomerular endothelial cells had swollen, separated from the glomerular basement membrane, and enlarged the sub endothelial space.[15] The evaluation criteria of efficacy were[16] CR: 24-hour urine protein quantification < 0.3 g, no activated urine sediment (urine erythrocyte count > 100,000 /mL or urine leukocyte > 5 /HP or erythrocyte tube type), serum albumin ≥ 35 g/L, sCr level normal or no higher than 15% of the baseline value; PR: decrease in the 24-hour urine protein quantification lower than 50% of the baseline value and < 3 g, serum albumin ≥ 30 g/L, and normal sCr or increase in sCr lower than 15% of the baseline value.

Statistical Analysis

Quantitative data are described as the mean ± standard deviation or median and interquartile range, as necessary. Student's t-test or the Mann–Whitney U test was performed to compare the differences between the two groups. Qualitative data are described as percentages and compared using the Fisher's exact test or chi-squared test. Prognosis was evaluated using Kaplan–Meier curves, and risk factors of TMA were identified using logistic regression. To analyse risk factors for renal failure, a Cox regression model was constructed. All data were processed using SPSS 21.0 (IBM Corporation, NY, USA), and $P < .05$ was defined as statistically significant.

RESULTS

Patient Characteristics

Of the 127 patients with LN enrolled in the study, 42 were in the LN-TMA group and 85 in the non-TMA group. Table 1 presents the comparison of the general data between the two groups. There were no significant differences in sex ($P > .05$) and age ($P > .05$) between the two groups. In the TMA group, 1 patient had TTP and 7 had history of using calcineurin inhibitors. No patient had haemolytic uremic syndrome, scleroderma, or malignant hypertension. Systolic blood pressure ($P < .05$), diastolic blood pressure ($P < .05$), blood urea nitrogen ($P < .001$), sCr levels ($P < .001$), TG ($P < .05$), and LDH ($P < .05$) were significantly higher in the LN-TMA group. The patients in the LN-TMA group had lower haemoglobin levels ($P < .05$), platelet levels ($P < .001$), and eGFR ($P < .05$) than those in the non-TMA group. The proportion of patients requiring dialysis during renal biopsy was significantly higher in the LN-TMA group ($P < .001$) than in the non-TMA group.

SLE-Specific and Renal Pathological Indicators

Table 2 shows the comparison of the indicators between the two groups. The SLEDAI score ($P < .05$), C3 ($P < .001$), and rates of pleurisy ($P < .001$) and

Table 1. Comparison of General Clinical Data

	TMA Group (n = 42)	Non-TMA Group (n = 85)	*P*
Age (years)	26.5 (20.75, 35)	27 (22, 40)	> .05
Sex (male/female)	6/36	9/76	> .05
SBP (mmHg)	140 (128, 155)	128 (117, 140)	< .01
DBP (mmHg)	93 ± 16	85 ± 14	< .01
Hb (g/L)	84.4 ± 20.14	99.38 ± 23.45	< .01
PLT ($\times 10^9$/L)	87 (59.75, 167.00)	155 (101.00, 220.00)	< .001
WBC ($\times 10^9$/L)	4.45 (3.15, 6.93)	4.90 (3.20, 7.20)	> .05
sCr (μmol/L)	157.75 (86.50, 311.50)	79.00 (62.00, 94.50)	< .001
BUN (mmol/L)	13.2 (8.1, 20.3)	7.5 (5.5,10.6)	< .001
eGFR (ml/min/1.73 m^2)	39.24 (14.66, 73.96)	97.40 (47.99, 118.84)	< .01
BNP (pg/ml)	8184 (2333, 35000)	2141 (887.25, 7075.89)	> .05
TG (mmol/L)	2.73 (1.48, 3.89)	2.07 (1.42, 2.88)	< .05
Cholesterol (mmol/L)	5.50 (4.40, 6.47)	5.05 (4.11, 6.08)	> .05
Alb (g/L)	26.33 ± 6.69	26.08 ± 6.55	> .05
LDH (U/L)	440 (248, 563)	236 (194, 364)	< .05
24hTP (g)	4.41 (1.78, 6.74)	3.61 (2.15, 6.70)	> .05
Patients of dialysis (%)	16 (38.1%)	2 (2.4%)	< .001

Abbreviations: TMA, thrombotic microangiopathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, haemoglobin; PLT, platelet; WBC, white blood cell; sCr, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; TG, triglyceride; Alb, albumin; LDH, lactic dehydrogenase; 24hTP, total urea protein for 24 hours.

Table 2. Comparison of Special Indicators and Renal Pathological Indexes

	TMA Group (n = 42)	Non-TMA Group (n = 85)	*P*
C3, g/L	3.62 (1.50, 11.25)	0.45 (0.32, 0.72)	< .001
C4, g/L	0.12 (0.06, 0.21)	0.10 (0.04, 0.15)	> .05
Anti-dsDNA, IU/mL	402.2 (32.3, 800)	575.4 (230.0, 800.0)	> .05
Anti-Sm (%)	13 (39%)	27 (47%)	> .05
ANA, mmol/L	295.1 (91.55, 300.0)	300.0 (156.3, 311.45)	> .05
Anticardiolipin IgG	2.45 (1.70, 4.51)	3.6 (2.08, 7.18)	> .05
Anticardiolipin IgM	3.95 (2.40, 5.80)	4.70 (2.13, 6.50)	> .05
SLEDAI Score	13.8 ± 3.4	10.88 ± 6.0	< .01
pulmonary Hypertension (%)	7 (17)	4 (4.7)	> .05
Pleurisy (%)	21 (50)	16 (18.8)	< .001
Pericarditis (%)	15 (36.6)	11 (12.9)	< .01
Renal AI	8.00 (6.25, 12.75)	2.00 (0.00, 7.00)	< .001
Renal CI	1.00 (0.00, 4.75)	4.00 (1.00, 8.00)	< .01
Class III or IV (%)	29 (69)	59 (69)	> .05
Class III + V or IV + V (%)	12 (29)	24 (28)	> .05
Class V (%)	1 (2)	2 (2)	> .05

Abbreviations: TMA, thrombotic microangiopathy.

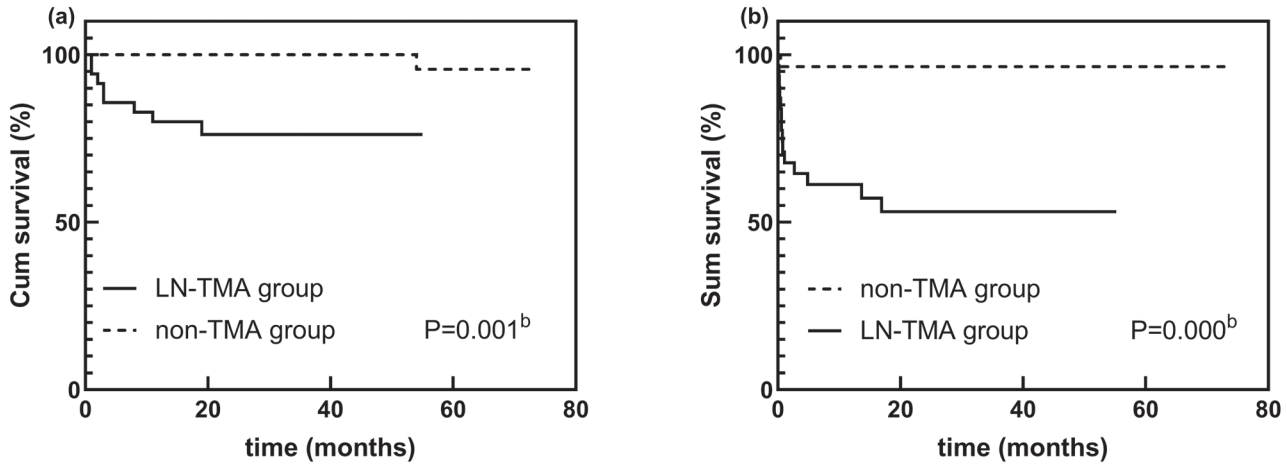
pericarditis ($P < .05$) were significantly higher in the LN-TMA group than in the non-TMA group. Anti-cardiolipin antibodies IgG ($P > .05$) and IgM ($P > .05$) were not significantly different between the two groups. In LN-TMA group, classes III and IV, classes III + V and IV + V, and class V accounted for 69%, 29%, and 2% of cases; respectively. The renal AI ($P < .001$) was significantly higher in the LN-TMA group than in the non-TMA group; however, the CI ($P < .05$) of the former was lower.

Prognosis and Follow-Up

After the follow-up of 48.09 ± 19.57 months and 24.13 ± 16.35 months in non-TMA and LN-TMA groups respectively, the patients in the LN-TMA group had significantly lower 3-year survival (76 vs. 94%, $P < .05$) and 3-year renal survival (44.5 vs. 94.7%, $P < .001$) rates than those in the non-TMA group (Figure). However, there were no significant differences in the PR or CR rates between the two groups (Table 3). By the end of follow-up, three of the eight patients who underwent plasmapheresis in the LN-TMA group had died, two were receiving regular haemodialysis, two had been discharged, and one had stopped haemodialysis.

Risk Factor Analysis

The analysis included the AI, CI, total urea



Comparison of Patient Survival (a) and Renal Survival (b) Between the LN-TMA Group and the Non-TMA Group (Abbreviations: LN, lupus nephritis; TMA, thrombotic microangiopathy).

Table 3. Comparison of 6-month and 12-month Remission Rates

	TMA Group (n = 42)	Non-TMA Group (n = 85)	*P*
PR (6 m)	6 (46%)	(63%)	> .05
PR (12 m)	5 (56%)	(52%)	> .05
CR (6 m)	2 (15%)	(26%)	> .05
CR (12 m)	2 (22%)	(48%)	> .05

Abbreviations: TMA, thrombotic microangiopathy; PR, partial remission; CR, complete remission.

protein for 24 hours (24hTP), and other laboratory indicators. Univariate cox regression analysis showed that TMA, AI, Alb, sCr levels, C-reactive protein (CRP), haemoglobin (Hb), platelets (plt), and SLEDAI scores were all risk factors for renal failure. These variables were included in the multivariate cox regression analyses; the results signalled that TMA (RR = 9.139; 95% CI: 2.60 to 32.13; $P < .05$) and sCr (RR = 1.002; 95% CI: 1.001 to 1.003; $P < .05$) were independent risk factors for renal failure. Logistic regression analyses showed that infection (95% CI: 0.001 to 0.125, $P < .05$), anti-ribosomal antibody (95% CI: 2.209 to 610.213, $P > .05$), and anti-histone antibody (95% CI: 0.000 to 0.312, $P < .05$) were risk factors for TMA in LN.

Effect of Plasmapheresis

There was no significant effect on LN-TMA. The C3 level in the LN-TMA group was significantly higher directly after plasmapheresis ($P < .05$) and 2 months after treatment ($P < .05$); however, there was no significant increase in platelets, Hb, or sCr levels between the groups (Table 4).

DISCUSSION

Previous studies have not been able to delineate the role of TMA in LN possibly because of sample-size and methodological limitations. To increase the credibility of our study, we matched the epidemiological and pathological types between the two groups and excluded diseases that may be confounding factors. In addition, this study gave a comprehensive description of LN-TMA from the basic characteristics, pathological features, survival rate, remission rate, and risk factors of renal failure to treatment, which is of great reference value for follow-up research. We found that symptoms, laboratory examination results, and pathological biopsies were worse in the LN-TMA group than in the non-TMA group. Although there was no significant difference between PR or CR rates, the patients in the LN-TMA group also had a lower remission rate than those in the non-TMA group. Additionally, the LN-TMA group had higher systolic and diastolic blood pressures, LDH, and blood lipids, and the rates of pleurisy and pericarditis were significantly higher than those in the non-TMA group. TMA was an independent risk factor for renal failure in LN. The levels of haemoglobin and platelets, however, were significantly lower in the TMA-LN than in the non-TMA group, indicating that LN-TMA not only influenced renal function but also substantially affected other organs. These findings suggest that LN-TMA is a special type that requires increased attention.

The incidence of LN-TMA varies across studies (1.4 to 24%).[15,17,18] In our study, classes III and IV accounted for 69%, classes III + V and IV + V for 29%, and class V for 2% of cases. These are consistent with the findings reported by previous studies.[14,15] This is undoubtedly worse for the already serious class III-V LN.

Studies have shown that the antiphospholipid antibody (aPL) is elevated in patients with SLE-TMA;[19,20] thus, many researchers believe that it is associated with TMA.[21-24] However, this finding could not be reproduced by other studies.[15,25,26] There were no significant differences in the anticardiolipin antibodies IgG and IgM between the two groups in our study. Moreover, only 35% of patients with LN-TMA had antiphospholipid syndrome (APS) despite it being common in TMA, highlighting the fact that TMA can be independent of APS.[27] The relationship between LN-TMA and APS, therefore, remains unclear. The occurrence

Table 4. Analysis of the Efficacy of Plasmapheresis in LN-TMA

	Before PE	After PE	*P*	2 Months After PE	*P*
Hb, g/L	87.57 ± 13.40	73.86 ± 14.95	> .05	100 (94.5, 116)	> .05
PLT, $\times 10^9$ /L)	75.29 ± 50.79	60.00 ± 32.57	> .05	88.00 ± 25.13	> .05
sCr, μmol/L	391.71 ± 232.14	316.54 ± 157.04	> .05	432.00 ± 201.68	> .05
C3, g/L	0.44 ± 0.19	0.63 ± 0.12	< .05	0.62 (0.58, 0.78)	< .05

Abbreviations: LN, lupus nephritis; TMA, thrombotic microangiopathy; Hb, haemoglobin; PLT, platelet; sCr, serum creatinine.

of TMA in LN may be multifactorial, implicating several mechanisms, such as those involving antibodies and complements.[28,29]

LN-TMA is often treated with a combination of glucocorticoid and immunosuppressive drugs or plasmapheresis if necessary. Although plasmapheresis has become the standard treatment for thrombotic thrombocytopenic purpura (TTP),[30] its efficacy in patients with LN-TMA is unknown. A retrospective study conducted by Li *et al.* found that additional plasmapheresis can effectively reduce the occurrence of endpoint events and is related to better prognosis.[31] Li *et al.* also confirmed that patients who underwent plasmapheresis exhibited a higher response rate, with fewer patients among them experiencing ineffective treatment.[32] However, a prospective study conducted by Pattanashetti *et al.* found no significant relief in patients with LN-TMA after additional plasmapheresis based on standard treatment.[33] No significant changes were observed in the clinical indicators before and after plasmapheresis in our study, and the efficacy was not apparent. These discrepancies may be associated with frequency and therapeutic dose, as performing plasmapheresis fewer than 7 times may be ineffective.[34] Chen *et al.* showed that patients who underwent more than 7 sessions of plasmapheresis had better outcomes and suggested that it should be continued until haemoglobin, platelet count, and sCr levels reach the normal range. Recently, the efficacy of eculizumab and rituximab on LN-TMA has attracted much attention. Benefits have been reported,[35] but mostly by case reports and small observational studies.[36] Moreover, studies have also shown that rituximab has no significant effect on renal survival,[37] thus its effect is speculative.

Eighty percent of patients with LN-TMA aged < 23 years progressed to ESRD within 5 years,[38] suggesting that identification of risk factors is paramount for effective evaluation of LN-TMA prognosis. In this study, baseline sCr levels and TMA were risk factors for renal failure. Other studies have also reported that aPLs,[39-41] decreased CFH, anti-dsDNA antibodies, and chronic characteristics of TMA were related to adverse renal results.[42,43] All the above information suggests that timely adjustments in therapeutic strategies are required to effectively delay disease progression. We also found that infection is a risk factor for TMA occurrence. It may participate in TMA by damaging endothelial cells, promoting blood coagulation, or activating complements. Additionally, many immunosuppressants can also accelerate the occurrence of TMA.[44,45] From this, we can infer that studies on LN accompanied by TMA should not only focus on its severity but also pay attention to the choice of medication and timely treatment of concomitant symptoms. This study is limited by its single centre retrospective nature. Because of the low incidence of LN-TMA and limitation of sample size, the experimental error may have been large; thus, overall generalisation to all patients cannot be performed. Further, as it's retrospective study, several parameters and treatment interventions could not be included in this study. In addition, because eculizumab and rituximab were not available in our centre at that time, we were unable to assess their effectiveness. Prospective, multi-centre studies are therefore needed to increase the sample size and obtain more reliable study data.

CONCLUSION

In conclusion, patients with LN-TMA have more severe clinical manifestations, higher renal failure rate and mortality. Future research efforts should investigate the underlying mechanisms of the condition with the aim of developing more effective prognostic indicators that may help formulate more effective treatment plans, reduce patient symptoms, and improve patient prognosis.

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CONFLICTS OF INTEREST / COMPETING INTERESTS

The authors declare that there is no conflict of interest.

ETHICS APPROVAL

The study was approved by our institutional review board.

CONSENT TO PARTICIPATE

The study was performed with the informed consent of the patients.

CONSENT FOR PUBLICATION

This study is agreed to publish.

EMBELLISHMENT

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