RESEARCH ARTICLE

Serum DNase1, sTNFR1 and sTNFR2 as Risk Factors for Lupus Nephritis in Systemic Lupus Erythematosus Patients

Ida Ayu Ratih Wulansari Manuaba[1,2,*], Ketut Suryana[3], I Made Bakta[2], I Made Sudarmaja[4]

[1]Doctoral Study Program in Medical Sciences, Faculty of Medicine, Universitas Udayana, Jl. P.B. Sudirman, Denpasar 80232, Indonesia
[2]Faculty of Health Sciences, Bali International University, Gg. Jeruk No.9A, Denpasar 80234, Indonesia
[3]Immunology Division, Department of Pulmonology, Faculty of Medicine, Universitas Udayana, Jl. P.B. Sudirman, Denpasar 80232, Indonesia
[4]Department of Parasitology, Faculty of Medicine, Universitas Udayana, Jl. P.B. Sudirman, Denpasar 80232, Indonesia

*Corresponding author. Email: idaayuratihwulansari@gmail.com

Received date: Apr 22, 2024; Revised date: Jun 8, 2024; Accepted date: Jun 12, 2024

Abstract

BACKGROUND: Early detection and management of lupus nephritis (LN) in systemic lupus erythematosus (SLE) are essential to prevent irreversible kidney damage and improve patient outcomes; therefore, identifying reliable biomarkers to predict LN is paramount. However, there are still relatively few studies examining the potential biomarkers for LN in SLE patients. This study was conducted to investigate serum deoxyribonuclease I (DNase), soluble tumor necrosing factor 1 (sTNFR1) and soluble tumor necrosing factor 2 (sTNFR2) as a risk factor for LN in SLE patients.
METHODS: A case-control study involving SLE patients aged 20-60 years was conducted. Blood was withdrawn from each subject for the measurement of serum level of DNase1, sTNFR1, and sTNFR2 that was performed using enzyme-linked immunoassay (ELISA) methods. Data was then analyzed using Chi-Square test and logistic regression tests.
RESULTS: A total of 22 patients with LN and 22 without LN were included. The cut-off value for DNase1, sTNFR1, and sTNFR2 were 5.05 ng/mL, 6.52 ng/mL, and 7.02 ng/mL, respectively. The risk factors of LN in SLE patients were the low level of serum DNase1 (aOR=6.64; 95%CI: 1.25-35.29; p=0.026), low level of serum sTNFR1 (aOR=8.12; 95% CI: 1.56-42.10; p=0.013), and low level of serum sTNFR2 (aOR=5.57; 95%CI: 1.03-30.11; p=0.046).
CONCLUSION: Serum DNase1 lower than 5.05 ng/mL, sTNFR1 lower than 6.52 ng/mL, and sTNFR2 lower than 7.02 ng/mL were risk factors for lupus nephritis in SLE patients. Hence, serum DNase1, sTNFR1 and sTNFR2 could be used as risk factors predictors for LN in SLE patients.
KEYWORDS: DNase1, sTNFR1, sTNFR2, SLE, lupus nephritis

Indones Biomed J. 2024; 16(3): 263-8

Introduction

Systemic lupus erythematosus (SLE) is an illness characterized by the development of antibodies that attack the body's tissues and can affect multiple organ systems, leading to a broad spectrum of clinical presentations. One of the most profound effects of SLE is lupus nephritis (LN), a condition where the immune initiates and attacks the kidneys, resulting in chronic inflammation and potentially leading to kidney failure. The prevalence of LN in SLE is reported to be around 40-70%.(1-3) The mortality rate of patients with LN in ten years is estimated to be as high as 30%. Approximately 13% of the survivors had end-stage renal disease (ESRD) that needs hemodialysis.(4) Early detection and management of LN are crucial to prevent irreversible kidney damage and improve patient outcomes. Identifying reliable biomarkers that can predict LN onset and progression is paramount in this context.

Deoxyribonuclease I (DNase1) is an enzyme that is involved in DNA degradation. It has been associated with the clearance of circulating nucleic acids and immune complex

formation in SLE. Its altered levels in serum may reflect disease activity and the propensity for organ involvement. Several studies have investigated a correlation between the activity of DNase1 and SLE in humans and animals. A study found that mice lacking the DNase1 gene do exhibit a phenotype similar to SLE.(5) DNase1 activity is seen to be reduced in patients with SLE compared to healthy control, and DNase1 shows an inverse relationship with disease activity, including LN.(6-8)

The pathophysiology of LN involves a multitude of immune mechanisms, where tumour necrosis factor (TNF)-α plays a significant role in mediating renal inflammation and damage. Both soluble tumour necrosis factor receptor (sTNFR)1 and sTNFR2 are soluble receptors that bind to TNF-α, an inflammatory cytokine implicated in inflammation and autoimmune pathology. These soluble receptors are thought to modulate TNF-α activity. The activity of sTNFR2 greatly enhances cellular stimulation, migration, and proliferation, while sTNFR1 works by initiating inflammation.(9) The expression levels of sTNFR1 and sTNFR2 significantly increase in the serum of patients with active SLE. A study found that the presence of high sTNFR1 was identified as a significant factor that increased the probability of renal damage in SLE.(10)

There are still relatively few studies that address DNase1, sTNFR1, and sTNFR2 as biomarkers for LN in SLE. The study that had been conducted in Indonesia investigating interleukin (IL)-6, IL-4, and interferon (IFN)-α as SLE biomarkers but not DNase1, sTNFR1, or sTNFR2.(11) Several authors address DNase1, sTNFR1, and sTNFR2 as biomarkers for LN in SLE, but in separated studies (5,7,8,12) or conducted in pediatric population (13). This current study compared and explored the combination of serum DNase1, sTNFR1, and sTNFR2 levels as risk factors in the pathomechanism of LN in adults with SLE. This study was conducted to investigate serum level DNase1, sTNFR1, and sTNFR2 as a risk factors predictors for LN in SLE patients.

Methods

Study Design and Subjects Recruitment

This was a case-control study conducted at the Biomedical Laboratorium, Faculty of Medicine, Universitas Udayana, Denpasar. The inclusion criteria for subjects were subjects aged between 20 to 60 years, diagnosed with SLE, and agreed to participate in the study. Diagnosis of SLE was made using the American College of Rheumatology (ACR) 1997 criteria.(14) LN was defined as a condition of persistent proteinuria greater than 0.5/day or greater than +3 if quantitation was not performed, or positive cellular cast (may be red cell, hemoglobin, granular, tubular or mixed). (15) Subjects who were pregnant, had diabetes mellitus, malignancy, infections, or terminal renal failure on dialysis were excluded.

The minimum sample calculation using 90% power and α=0.05 were 20 samples in each group. To avoid dropout, we added 10% of the minimum samples. Therefore, a total of 44 subjects were recruited in this study. Study subjects were consecutively enrolled and signed a written informed consent form. The research protocol was approved by the Ethics Committee of Medical Faculty, Universitas Udayana (0143/UNl4.2.2.VII.14 /LT) in 2024.

DNase-1, sTNFR1 and sTNFR2 Measurement

Around 3 mL of blood serum was obtained from venapuncture at the antecubital vein and drained for the measurement of serum DNase-1, sTNFR1 and sTNFR2 level. Measurement of DNase1 serum level was conducted using an enzyme-linked immunosorbent assay (ELISA) methods, which the procedure and technique was performed according to the kit manual of Human DNase1 ELISA kit (Cat. No. E0876Hu; Bioassay Technology Laboratory, Jiaxing, China). The plate was pre-coated with a Human DNase-1 antibody. When DNase-1 antigen was added, it would binds to antibodies coated on the wells. The Biotinylated Human DNase-1 Antibody was added and bound to DNase-1 in the sample. Then Streptavidin-HRP was added and bound to the Biotinylated DNase-1 antibody. After incubation, unbound Streptavidin-HRP was washed away during a washing step. Substrate solution was then added and color developed in proportion to the amount of Human DNase-1. The reaction was terminated by the addition of an acidic stop solution and absorbance was measured at 450 nm.

The measurement of the sTNFR1 and sTNFR2 serum level were performed using the Human TNFR1 ELISA kit (Cat. No. E4351Hu; Bioassay Technology Laboratory) and Human TNFR2 ELISA kit (Cat. No. E4749Hu; Bioassay Technology Laboratory), respectively. The procedure and technique were similar with the DNase1 ELISA kit.

Statistical Analysis

Data analysis was conducted using IBM SPSS version 23 for the Windows operating system (IBM Corporation, Armonk, NY, USA). The cut-off level of all biomarkers was determined through the median. Bivariate analysis

employed the Chi-Square test, whereas multivariate analysis proceeded with multiple logistic regression tests. The results were deemed statistically significant if the p-value was less than 0.05.

Results

Characteristics of Study Subjects

There were 22 patients in both cases group and in the control group. The majority of the patients were dominated by females, namely 41 (93.18%) patients. In terms of age, all of the study subjects were in the age range between 20-60 years. In terms of general Anti Nuclear Antibody Immunofluorescence (ANA IF) titers results from all research subjects, the most common pattern was 1:100 speckled and 1:1000 speckled. All research subjects had been diagnosed with SLE, where 50% of subjects had been diagnosed with SLE for less than five years. When the research was underway, all research subjects were still routinely consuming pharmacological therapy given by the doctor in charge of the patient as an immunosuppressant, with the most basic treatment chosen to be hydroxychloroquine drugs (88.6%). Routine haematological examination revealed most of the subjects were normal. All subject characteristic data can be seen in Table 1.

Table 1. Characteristics of study subjects.

Variables	n (%)
Gender	
Male	3 (6.9)
Female	41 (93.1)
ANA IF	
1: 80 homogenous	1 (2.3)
1: 100 speckled	9 (20.5)
1: 100 homogenous	4 (9.1)
1: 320 speckled	8 (18.1)
1: 320 nuclear homogenous	5 (11.4)
1: 1000 speckled	9 (20.5)
1: 1000 nuclear homogenous	8 (18.1)
SLE duration (years)	
1-5	22 (50.0)
6-10	17 (38.6)
11-15	4 (9.1)
16-20	1 (2.3)
Hematology result	
Anemia	14 (31.8)
Leukopenia	4 (9.1)
Lymphopenia	4 (9.1)
Normal	22 (50.0)
Medication during study	
Corticosteroid	33 (75.0)
Antimalaria	39 (88.6)
Mycophenolate	26 (59.0)
Azathioprine	6 (13.6)
Methotrexate	2 (4.5)
Leflunomide	3 (6.8)
Nutritional status (kg/m^2)	
<17	1 (2.3)
17-18.5	7 (15.9)
18.5-24.9	18 (40.9)
25-29.9	18 (40.9)

Serum DNase1, sTNFR1 and sTNFR2 as Risk Factors for LN in SLE Patients

The levels of DNase1, sTNFR1, and sTNFR2 were classified into low and high based on their median. A cut-off value of serum DNase1, sTNFR1, and sTNFR2 as biomarkers for LN in SLE patients was shown in Table 2. The Chi-square test revealed that serum DNase1 lower than 5.05 ng/mL increased the risk of LN development in SLE up to nine times higher (OR= 9.06; 95%CI: 2.3-35.6; p=0.001). In addition, SLE patients with sTNFR1 lower than 6.52 ng/mL had higher risk of LN development compared to SLE patients with sTNFR1 higher than 6.52 ng/mL (OR= 11.56; 95%CI: 2.82-47.3; $p\leq$0.001). We also found that sTNFR2 lower than 7.02 ng/mL were associated with increased risk of LN in SLE patients (OR= 4.59; 95%CI: 1.29-16.33; p=0.016) (Table 3).

Multivariate Analysis

Multivariate analysis further confirmed that the strongest predictor as risk factor of LN in SLE patients were sTNFR1 lower than 6.52 ng/mL (aOR=8.12; 95%CI: 1.56-42.10; p=0.013), serum DNase1 lower than 5.05 ng/mL (aOR=6.64; 95%CI: 1.25-35.29; p=0.026), and sTNFR2 lower than 7.02 ng/mL (aOR=5.57; 95%CI: 1.03-30.11; p=0.046) (Table 4).

Discussion

This study showed that low levels of serum DNase1 are a predictor of LN in SLE patients. This finding aligned with a multicenter study in Argentina that reported that DNase1 gene polymorphism was related to a double chance of developing nephritis in SLE patients.(16) Another study in 45 SLE patients found that The DNase1 activity was significantly lower in active LN than in a clinically stable phase.(7) One study reported that DNase1 activity in people

Table 2. Cut-off value of serum DNase1, sTNFR1, and sTNFR2 as biomarkers for LN in SLE patients.

Variables	Cut-off Value	Min - Max
DNase1 (ng/mL)	5.05 (median)	3.53 - 71.25
sTNFR1 (ng/mL)	6.52 (median)	3.02 - 50.05
sTNFR2 (ng/mL)	7.02 (median)	2.47 - 43.01

with SLE was lower than that of individuals without SLE. In addition, DNase1 activity positively correlates with disease burden and antibodies in SLE.(8)

DNase1 is an enzyme responsible for degrading extracellular DNA. The reduction in DNase1 activity could contribute to the accumulation of DNA-containing immune complexes in the glomeruli, promoting inflammation and tissue damage in the kidneys.(6,17,18) Reduced DNase1 activity is associated with inadequate removal of apoptotic cells, resulting in the debris of chromatin fragments and more cells undergoing secondary necrosis.(19) Cells that undergo necrosis will release their intracellular content and may trigger an inflammation cascade. This event may also promote dendritic cells to their maximum antigen-presenting capacity. The triggered immune response occurred mostly in the kidney, where DNase1 controlled more than eighty percent of the endonuclease enzyme activity.(20) Therefore, reduced DNase1 activity can commence the development of LN in SLE patients.(7)

This study revealed that serum sTNFR1 was the strongest predictor as risk factor of LN in SLE patients. Several studies were supported this resulted, that the average level of serum sTNFR1 was greater in the LN group than in both the inactive LN and non-LN groups in SLE patients, serum sTNFR1 was also correlated with SLEDAI scores.(12) Other study was reported, that plasma sTNFR1 was higher in the LN group than in the non-LN cohort, and sTNFR1 was a significant risk factor for LN. In addition, sTNFR1 was the risk factor for more severe SLE disease activity, decline of renal function, and proteinuria in LN patients.(21,22)

The higher levels of sTNFR1 in SLE patients with LN may reflect an upregulation of the TNF-α signalling pathway, contributing to LN inflammatory milieu and kidney damage characteristic. TNF-α is an inflammatory mediators that would attract macrophages infiltration into extracellular matrix.(23) The mechanism of sTNFR1 in LN was hypothesised to be direct damage caused by activated inflammatory responses by sTNFR1, chronic inflammation is thought to contribute the decline in renal function. There was one study found that proliferative LN, glomerular TNFRI level and sTNFR1 expression in renal tubular epithelial cells were significantly elevated.(21)

Serum sTNFR2 was also a predictor risk factor for LN in this study. This was in line with a previous study that showed sTNFR2 levels were higher in SLE patients with active LN than those without LN or with inactive LN or without SLE. (24-27) One study reported that sTNFR2 levels in LN were higher than healthy control. Furthermore, sTNFR2 level fall six months after LN treatment in proliferative LN. However, in the membranous LN group, only drug responders in LN showed a drop in sTNFR2 levels; non-drug-responders did not show this same trend. During long-term follow-up, the sTNFR2 levels were linked to declining kidney function and were higher in patients with CKD stage ≥3 compared to stages 1 and 2.(24) A study resulted also discovered increased levels of sTNFR2 in patients with LN compared to non-LN, and sTNFR2 was an independent marker for SLE disease activity.25 The level of sTNFR2 was higher in juvenile SLE compared to healthy control. Still, there was no significant difference in sTNFR2 between active LN and inactive LN in pediatric patients. However, sTNFR2 was positively correlated with erythrocyte sedimentation rate (ESR) and anti-dsDNA antibodies.(13) The disparity in the results of this study may be attributed to the difference in the age of the samples. Consequently, further investigation is

Table 3. Serum DNase1, sTNFR1, and sTNFR2 as biomarkers for LN in SLE patients.

Variable	Category	Group		Total	OR	95% CI		*p*-value
		LN	Non-LN			Lower	Upper	
DNase1 (Cut-off: 5.05)	Low	17 (73.9)	6 (26.1)	23 (100)	9.067	2.306	35.650	0.001
	High	5 (23.8)	16 (76.2)	21 (100)				
sTNFR1 (Cut-off: 6.52)	Low	17 (77.3)	5 (22.7)	22 (100)	11.560	2.822	47.356	0.000
	High	5 (22.7)	17 (77.3)	22 (100)				
sTNFR2 (Cut-off: 7.02)	Low	15 (68.2)	7 (31.8)	22 (100)	4.592	1.291	16.331	0.016
	High	7 (31.8)	15 (68.2)	22 (100)				

Table 4. Multivariate Analysis of Serum DNase1, sTNFR1, and sTNFR2 as biomarkers for LN in SLE patients.

Variable	*p*-value	Adjusted OR	95% C.I.for EXP(B)	
			Lower	Upper
DNasel (low)	0.026	6.646	1.252	35.296
sTNFR1 (low)	0.013	8.127	1.569	42.102
sTNFR2 (low)	0.046	5.572	1.031	30.118

required to determine the relevance of LN and SLE disease activity biomarkers in pediatric patients.

This elevation of sTNFR2 reflects LN heightened inflammatory state and immune system activation. The sTNFR2, by binding to circulating TNF-α, can serve as a buffer to modulate the biological effects of TNF-α. Still, its increased levels might also be a marker of TNF-α overproduction and ongoing inflammation. The molecular mechanism of sTNFR2 in causing renal injury and damage is hypothesised due to its role in glomerular complement deposition and activation of TNF-α, which stimulates monocyte chemoattractant protein-1 (MCP-1).(24) The expression of sTNFR2 will increase in glomerular and tubular cells when there is a local inflammation. The expression of sTNFR2 in the kidneys was crucial for developing proteinuria and glomerulonephritis, leading to glomerular complement deposition. sTNFR2 was found to play an essential role in facilitating the impact of TNF-α on MCP-1 production, while sTNFR1 did not seem to be implicated in this event.TNF-α was revealed to have a significant effect on podocytes, leading to the production of MCP-1.(26,28) In addition, research has shown that the level of MCP-1 can indicate a negative renal prognosis in LN.(29,30) Nevertheless, the reasons behind sTNFR2's increased presence in renal tissue remain to be fully understood.

This study has several limitations. First, as we use ACR criteria for diagnosing SLE, individuals who have recently developed or exhibit less prevalent symptoms may not be identified.(31) Second, other biomarkers (*e.g.*, VEGF) are still not being compared in this study. Third, we didn't analyse the confounding variables such as sosioeconomic and medication factors. Lastly, renal involvement in lupus nephritis was not confirmed by renal biopsy. It is advised to conduct further diagnostic studies to determine the cut-off values for DNase1, sTNFR1, and sTNFR2 levels. Cohort studies are also advised to ascertain alterations in the fluctuating levels of sTNFR1 and sTNFR2 in LN. Additional research is required to completely clarify the mechanisms that underlie the association between DNase1, sTNFR1, and sTNFR2 with LN and to determine the clinical utility of those biomarkers in routine practice. Study in various age groups, such as adolescents under 20, and divide groups by renal SLEDAI is also recommended.

Conclusion

The results of this investigation indicate that serum DNase1 lower than 5.05 ng/mL, sTNFR1 lower than 6.52 ng/mL, and sTNFR2 lower than 7.02 ng/mL were risk factors for lupus nephritis in SLE patients. Hence, serum DNase1, sTNFR1 and sTNFR2 could be used as risk factors predictors for LN in SLE patients.

Authors Contribution

IARWM planned the study, gathered the data, conducted the analysis, and composed the article draft. KS, IMB, and IMS provided crucial revisions for the methods and manuscript. All authors have reviewed and accepted the final paper.

References

1. Mahajan A, Amelio J, Gairy K, Kaur G, Levy RA, Roth D, *et al.* Systemic lupus erythematosus, lupus nephritis and end-stage renal disease: A pragmatic review mapping disease severity and progression. Lupus. 2020; 29(9): 1011-20.
2. Lanata CM, Nititham J, Taylor KE, Chung SA, Torgerson DG, Seldin MF, *et al.* Genetic contributions to lupus nephritis in a multi-ethnic cohort of systemic lupus erythematous patients. PLoS One. 2018; 13(6): e0199003. doi: 10.1371/journal.pone.0199003.
3. Elsisi GH, Hsieh SC, Chen DY. The economic burden of systemic lupus erythematosus in Taiwan. J Med Econ. 2024; 27(Suppl1): 56-66.
4. Hocaoğlu M, Valenzuela-Almada MO, Dabit JY, Osei-Onomah SA, Chevet B, *et al.* Incidence, prevalence, and mortality of lupus nephritis: A population-based study over four decades using the lupus midwest network. Arthritis Rheumatol. 2023; 75(4): 567-73.

5. Kenny EF, Raupach B, Abu Abed U, Brinkmann V, Zychlinsky A. Dnase1-deficient mice spontaneously develop a systemic lupus erythematosus-like disease. Eur J Immunol. 2019; 49(4): 590-9.
6. Martinez-Valle F, Balada E, Ordi-Ros J, Bujan-Rivas S, Sellas-Fernandez A, Vilardell-Tarres M. DNase 1 activity in patients with systemic lupus erythematosus: relationship with epidemiological, clinical, immunological and therapeutical features. Lupus. 2009; 18(5): 418-23.
7. Martinez-Valle F, Balada E, Ordi-Ros J, Bujan-Rivas S, Sellas-Fernandez A, Vilardell-Tarres M. DNase1 activity in systemic lupus erythematosus patients with and without nephropathy. Rheumatol Int. 2010; 30(12): 1601-4.
8. Skiljevic D, Jeremic I, Nikolic M, Andrejevic S, Sefik-Bukilica M, Stojimirovic B, *et al.* Serum DNase I activity in systemic lupus erythematosus: correlation with immunoserological markers, the disease activity and organ involvement. Clin Chem Lab Med. 2013; 51(5): 1083-91.
9. Richter P, Macovei LA, Mihai IR, Cardoneanu A, Burlui MA, Rezus E. Cytokines in systemic lupus erythematosus-focus on TNF-α and IL-17. Int J Mol Sci. 2023; 24(19): 14413. doi:10.3390/ijms241914413.
10. Ghorbaninezhad F, Leone P, Alemohammad H, Najafzadeh B, Nourbakhsh NS, Prete M, *et al.* Tumor necrosis factor-α in systemic lupus erythematosus: Structure, function and therapeutic implications (Review). Int J Mol Med. 2022; 49(4): 43. doi:10.3892/ijmm.2022.5098.
11. Suntoko B, Hadisaputro S, Kalim H, Hadi S, Warlisti IV. A double-blind, randomized controlled trial of hydroxychloroquine for cognitive dysfunction and inflammatory biomarkers in systemic lupus erythematosus patients in Indonesia. Indones Biomed J. 2023; 15(4): 354-61.
12. Adhya Z, El Anbari M, Anwar S, Mortimer A, Marr N, Karim MY. Soluble TNF-R1, VEGF and other cytokines as markers of disease activity in systemic lupus erythematosus and lupus nephritis. Lupus. 2019; 28(6): 713-21.
13. Patel M, Oni L, Midgley A, Smith E, Tullus K, Marks SD, *et al.* Increased concentration of plasma TNFR1 and TNFR2 in paediatric lupus nephritis. Lupus. 2016; 25(9): 1040-4.
14. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997; 40(9): 1725. doi: 10.1002/art.1780400928.
15. Smith EL, Shmerling RH. The American College of Rheumatology criteria for the classification of systemic lupus erythematosus: Strengths, weaknesses, and opportunities for improvement. Lupus. 1999; 8(8): 586-95.
16. Camicia G, Muñoz SA, Allievi A, Orden AO, Perés Wingeyer S, *et al.* Association between severe disease course and nephritis with Q222R polymorphism in DNAse I gene among lupus patients: An Argentine multicenter study. Acta Reumatol Port. 2016; 41(2): 138-44.
17. Felux J, Erbacher A, Breckler M, Hervé R, Lemeiter D, Mannherz HG, *et al.* Deoxyribonuclease 1-mediated clearance of circulating chromatin prevents from immune cell activation and pro-inflammatory cytokine production, a phenomenon amplified by low trap1 activity: Consequences for systemic lupus erythematosus. Front Immunol. 2021; 12: 613597. doi: 10.3389/fimmu.2021.613597.
18. Hakkim A, Fürnrohr BG, Amann K, Laube B, Abed UA, Brinkmann V, *et al.* Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci USA. 2010; 107(21): 9813-8.
19. Engavale M, McCord J, Mapp B, Nzimulinda N, Bengtson E, Sutton RB, *et al.* Dnase1 Family in Autoimmunity. Encyclopedia. 2021; 1(3): 527-41.
20. Zykova SN, Tveita AA, Rekvig OP. Renal Dnase1 enzyme activity and protein expression is selectively shut down in murine and human membranoproliferative lupus nephritis. PLoS One. 2010; 5(8): e12096. doi: 10.1371/journal.pone.0012096.
21. Liu XR, Qi YY, Zhao YF, Cui Y, Zhao ZZ. Plasma soluble tumor necrosis factor receptor I as a biomarker of lupus nephritis and disease activity in systemic lupus erythematosus patients. Ren Fail. 2023; 45(1): 2174355. doi: 10.1080/0886022X.2023.2174355.
22. Zheng CZ, Yan WW, Luo YL, Wang TL, Shu YB. Value of sTNF-R1 and linc0597 as indicators for disease activity and diagnosis of lupus nephritis. Eur Rev Med Pharmacol Sci. 2020; 24(10): 5582-91.
23. Kartika R, Wibowo H. Impaired function of regulatory T cells in type 2 diabetes mellitus. Mol Cell Biomed Sci. 2020; 4(1): 1-9.
24. Parodis I, Ding H, Zickert A, Arnaud L, Larsson A, Svenungsson E, *et al.* Serum soluble tumour necrosis factor receptor-2 (sTNFR2) as a biomarker of kidney tissue damage and long-term renal outcome in lupus nephritis. Scand J Rheumatol. 2017; 46(4): 263-72.
25. Mahmoud RAK, El-Gendi HI, Ahmed HH. Serum neopterin, tumor necrosis factor-alpha and soluble tumor necrosis factor receptor II (p75) levels and disease activity in Egyptian female patients with systemic lupus erythematosus. Clin Biochem. 2005; 38(2): 134-41.
26. Vielhauer V, Stavrakis G, Mayadas TN. Renal cell-expressed TNF receptor 2, not receptor 1, is essential for the development of glomerulonephritis. J Clin Invest. 2005; 115(5): 1199-209.
27. Lousa I, Reis F, Santos-Silva A, Belo L. The signaling pathway of TNF receptors: Linking animal models of renal disease to human CKD. Int J Mol Sci. 2022; 23(6): 3284. doi: 10.3390/ijms23063284.
28. Chung CH, Fan J, Lee EY, Kang JS, Lee SJ, Pyagay PE, *et al.* Effects of tumor necrosis factor-α on podocyte expression of monocyte chemoattractant protein-1 and in diabetic nephropathy. Nephron Extra. 2015; 5(1): 1-18. doi: 10.1159/000369576.
29. Marks SD, Williams SJ, Tullus K, Sebire NJ. Glomerular expression of monocyte chemoattractant protein-1 is predictive of poor renal prognosis in pediatric lupus nephritis. Nephrol Dial Transplant. 2008; 23(11): 3521-6.
30. Xia YR, Li QR, Wang JP, Guo HS, Bao YQ, Mao YM, *et al.* Diagnostic value of urinary monocyte chemoattractant protein-1 in evaluating the activity of lupus nephritis: a meta-analysis. Lupus. 2020; 29(6): 599-606.
31. Surjawan Y, Intansari US. Suggested rational considerations for ANA-IF and ENA-profile test requisition: Clinical manifestation, gender, pattern, and riter of ANA-IF. Indones Biomed J. 2023; 15(3): 253-61.