Predictors and risk factors of lupus nephritis in a cohort of Egyptian systemic lupus erythematosus patients

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Abstract

Aim of the work: To evaluate the risk factors and predictors for the development of lupus nephritis (LN); and for non-remitting LN in a cohort of Egyptian systemic lupus erythematosus (SLE) patients.

Patients and methods: The current study was a retrospective and prospective follow up study of 250 SLE patients, who had been following up during the period between 2000 and 2021 at Rheumatology and Rehabilitation department, Kasr Al Ainy hospital, Cairo university. Patients choice based on those who presented with SLE from year 2000 to year 2009 with subsequent 12 years of follow up. This study was categorized into 3 stations: ***Station 1 (***SLE diagnosis), ***Station 2*** (development *of* LN) and ***Station 3*** (two years for LN management).

Results: **69.6%** of SLE patients developed LN. After 2 years of management of LN, **73.6%** of LN patients achieved complete renal remission while **26.4%** patients did not**.** The significant predictors for LN were juvenile onset SLE, constitutional manifestations, obstetric complications, hypocomplementemia (C3), anti-dsDNA and severe disease activity. Predictors for non-remitting LN were active with chronic or chronic lesions in renal biopsy, recurrent infections, pregnancy and constitutional manifestations in 3rd station**.**

Conclusion: Predictors for LN development were juvenile onset SLE, constitutional manifestations, obstetric complications, hypocomplementemia (C3), anti-dsDNA antibodies and severe disease activity. Predictors for non-remitting LN were active with chronic or chronic lesions in renal biopsy, recurrent infections, pregnancy and constitutional manifestations in 3rd station**.**

Keywords: Systemic lupus erythematosus (SLE), Lupus nephritis (LN), Remission, Relative Risk (RR), Predictors.

Statements and Declarations

Conflict of interest**:** none

Funding**:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune, multisystem and multifactorial disease, which is known in medicine as the great imposter because of its extremely diverse clinical presentations. SLE is unique among other autoimmune disorders, due to it has an unpredictable clinical course and it can directly affect any organ **[1].**

Renal involvement is common in SLE **[2]**, it is a serious complication and a major cause of morbidity and mortality in SLE **[3].** Lupus nephritis (LN) occurs in up to 35% of adults with SLE at the time of diagnosis, with an estimated total of 50–60% developing LN during the first 10 years of disease **[4].** It is estimated that approximately 90% of SLE patients will have pathologic evidence of renal involvement on biopsy, but only 50% will develop clinically significant nephritis **[5]**. Early diagnosis and treatment of renal condition are important since delayed diagnosis is a risk factor for end stage renal disease (ESRD) **[3].** Overall survival in patients with SLE is approximately 95% at 5 years after diagnosis and 92% at 10 years after diagnosis. The presence of LN significantly reduces survival to 88% at 10 years **[4].**

Patients and methods

This study was conducted on 250 patients with SLE diagnosed according to the American College of Rheumatology (ACR) 1997 revised criteria for the classification of SLE **[6]**, who followed retrospectively and prospectively during the period between 2000 and 2021 at the Rheumatology and Rehabilitation department, Kasr Al Ainy hospital, Cairo university. To be included in the study, patients should be presented with lupus in years from 2000 to 2009 with subsequent 10 years of follow up to detect LN development. Additional 2 years were added after the commencement of LN management to assess response of treatment and prognosis. The study period was from 2019 to 2021.

Exclusion criteria were: patients who were initially presenting with LN, comorbidities (hypertension (HTN), diabetes mellitus and cardiac disease), lost follow up for more than one year or disease duration less than 10 years. The study has been approved by the local ethics committee approval code MD-10-2019. Informed consent was obtained from all individual participants included in the study.

Collection, storage and the use of clinical and laboratory data were conducted in accordance to the chosen points: ***station 1:*** The baseline station for all SLE patients included in the study. It represented the first systemic lupus disease diagnosis. ***Station 2***: The 1st time of diagnosis of LN throughout the proposed 10 years of the follow up according to ACR criteria **[4].** ***Station 3:*** The period of 2 years of follow up of LN patients group after the commencement of LN management; to assess response of treatment according to the EULAR recommendations for the management of SLE **[7]**.

The following data were collected**: At the 1st Station:** Age, sex, constitutional, mucocutaneous, musculoskeletal, pulmonary, cardiac, neuropsychiatric, hematological, gastrointestinal (GIT), antiphospholipid syndrome (APS) manifestations, complete blood count (CBC), serum creatinine, urea, transaminases (ALT and AST), serum albumin, erythrocyte sedimentation rate (ESR), anti-nuclear antibodies (ANA), anti-double stranded DNA (anti-dsDNA) antibodies, complement component levels (C3 and C4), aPL profile (LA, anti-B2GP1 and aCL antibodies) and assessment of disease activity using SLE disease activity index **(**SLEDAI) . **At 2nd Station:** Age of patients at the development of LN, the time interval between the onset of SLE and the development of LN, clinical presentation of LN (HTN and lower limb edema), laboratory features include (creatinine, urea, serum albumin, complement component levels (C3 and C4), complete urine analysis (pyuria, hematuria and cellular casts whether RBCs or WBCs casts) , 24 hour urinary protein, renal biopsy, associated disease manifestations and SLEDAI Score. **At 3rd Station:** Treatment

(management of LN include induction therapy either by cyclophosphamide (CYC) or mycophenolate mofetil (MMF), maintenance therapy (by MMF or azathioprine (AZA)), hydroxychloroquine (HCQ), antiproteinuric drugs (e.g. a*ngiotensin-converting enzyme* (*ACE*) *inhibitors*) and other treatment (e.g. anticoagulant)), regularity on treatment, associated disease manifestations, recurrent infections and occurrence of pregnancy despite of contraception.

Complete renal remission was defined as UPr<500 mg/24 hours and SCr within 10% from baseline, according to the 2019 EULAR recommendations for the management of SLE **[7]**.

Statistical methods:

Data were statistically described in terms of mean±standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Student *t* test for independent samples in comparing normally distributed data/large enough samples, and Mann Whitney *U* test for independent samples for comparing not-normal data. Within group comparison of numerical variables was done using paired *t* test in comparing normally distributed data/large enough samples, and Wilcoxon signed rank test for paired (matched) samples when data are not normally distributed. For comparing categorical data, Chi-square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. The relative risk (RR) with 95% confidence intervals (CI) was calculated. Multivariate regression analysis was used to determine the significant independent predictors of occurrence of LN and occurrence of non-remission. Two-sided *p* values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release22for Microsoft Windows.

Results:

A total of 250 SLE patients included in the study, **174 (69.6%)** patients developed LN and **76 (30.4%)** patients did not develop LN. Most of LN patients were females (90.2%) while (9.8%) were males and their mean age was 22.8±8.2 years at the onset of SLE.

Relative risk was done based on data of the **1st Station.** Relative risk with 95% confidence interval showed that: each of juvenile onset SLE, the presence of constitutional and cardiac manifestations especially pericardial effusion and coronary artery disease were carried one and half times higher risk to develop LN and this was statistically significant **(RR=1.26, 1.29, 1.36, 1.34, 1.44) (CI=1.062- 1.497, 1.067-1.568, 1.149-**

1.612, 1.105- 1.62, 1.329- 1.569) respectively**.** As regards the serological and immunological profile, hypocomplementemia (C3 and C4) carried one and half times higher risk for the development of LN and this was statistically significant **(RR=1.48, 1.44) (CI=1.24-1.785, 1.219-1.7)** respectively**.** Interestingly, positive anti-dsDNA antibody test carried 3 times higher risk for the development of LN and this was statistically significant **(RR=3.125) (CI=2.189-4.461) (Table-1).**

On the other hand, the presence of each of mucocutaneous and musculoskeletal manifestations in the form of arthralgia, arthritis and hematological manifestations especially leucopenia were protective factors against the development of LN and this was statistically significant **(RR=0.73, 0.82, 0.77, 0.779, 0.78**, **0.749**) **(CI= 0.633-0.842, 0.678-0.991, 0.657- 0.903, 0.667- 0.908, 0.631- 0.965, 0.564- 0.993)** respectively **(Table-1)**.

Table-1: Relative risk for LN development.

Variables	RR	95% CI
Demographic Features		
Sex (male)	1.18	0.942- 1.479
Age of the onset of SLE (Juvenile onset)	**1.26**	**1.062-1.497**
Clinical Features		
Constitutional manifestations	**1.294**	**1.067- 1.568**
Mucocutaneous manifestations	**0.731**	**0.633-0.842**
Malar rash	1.175	0.685-2.015
Discoid rash	0.595	0.183-1.939
Photosensitivity	0.719	0.416-1.242
Oral/Nasal ulcer	0.586	0.338-1.015
Alopecia	0.828	0.48-1.43
Livedo reticularis	0.214	0.019-2.395
Raynaud's	0.853	0.402-1.811
Dry eye/ mouth	0.86	0.51-1.451
Vasculitis	0.906	0.653- 1.2576
Musculoskeletal manifestations	**0.82**	**0.678-0.991**
Arthralgia	**0.77**	**0.657- 0.903**
Arthritis	**0.779**	**0.667- 0.908**
Pulmonary manifestations	0.969	0.805- 1.166
Pleurisy	0.969	0.805- 1.166

Pleural effusion	1.23	0.96- 1.575
Cardiac manifestations	**1.36**	**1.149- 1.612**
Pericardial effusion	**1.34**	**1.105- 1.62**
CAD	**1.444**	**1.329- 1.569**
Serositis	1.02	0.856- 1.219
Neurological manifestations	1	0.801- 1.374
Hematological manifestations	**0.78**	**0.631- 0.965**
Hemolytic anemia	0.884	0.667- 1.172
Leucopenia	**0.749**	**0.564- 0.993**
Thrombocytopenia	0.699	0.456- 1.07
GIT manifestations	1.122	0.783- 1.607
APS syndrome	0.884	0.667- 1.172
Obstetric complications	0.914	0.685- 1.221
Arterial /Venous thrombosis	0.609	0.257- 1.438
Laboratory Features		
ESR	1.102	0.934- 1.3
Urea	1.185	0.885- 1.585
Serum albumin	0.936	0.738-1.187
C3	**1.487**	**1.24-1.785**
C4	**1.442**	**1.219-1.7**
Immune Profile		
Anti-dsDNA	**3.125**	**2.189-4.461**
Anti RO	1.112	0.83-1.491
Anti LA	1.3	0.969- 1.744
Total APL profile	0.979	0.83- 1.155
SLEDAI Score		
Disease activity	0.931	0.772- 1.122

RR: relative risk, CI: confidence interval, CAD: Coronary artery disease, GIT: Gastrointestinal, APS: Antiphospholipid syndrome, SLEDAI: SLE Disease Activity Index, ESR: Erythrocyte sedimentation rate, C: Complement, Anti-dsDNA: anti-double stranded DNA.

RR=1 means that event is equally likely in both groups, RR>1 means that event is more likely in LN group and RR <1 means that event is less likely in LN group.

As regards the predictors of LN, multivariate logistic regression analysis was done to determine the significant predictors of the occurrence of LN based on data of **1st Station .**

The presence of each of: juvenile onset SLE, constitutional manifestations, obstetric complications, hypocomplementemia (C3), anti-dsDNA antibodies and severe disease activity using SLEDAI were predictors of the development of LN **(P=0.041, 0.03, 0.039, 0.024, 0.028, 0.012)** respectively. In the contrary,

Adult onset SLE, mucocutaneous manifestations, arthralgia, arthritis and mild disease activity were protective factors against the development of LN **(P=0.041, 0.001, 0.036, 0.019, 0.025)** respectively **(Table-2)**.

Table-2: Predictors for LN development.

Variables		B Coefficient	95% CI	P-Value
Demographic Features				
Sex	**Female**	-0.123	(-0.33, 0.08)	0.239
	Male	0.123	(-0.08, 0.33)	0.239
Age of the onset of SLE	**Juvenile onset**	0.175	(0.007,0.344)	**0.041***
	Adult onset	-0.175	(-0.344, -0.007)	**0.041***
Clinical Features				
Constitutional manifestations		0.211	(0.02,0.402)	**0.03***
Fever		-0.099	(-0.267,0.07)	0.265
Fatigue		0.056	(-0.097,0.21)	0.471
Weight loss		-0.092	(-0.303,0.12)	0.385
Mucocutaneous manifestations		-0.324	(-0.513,-0.134)	**0.001****
Malar rash		0.141	(0.002,0.28)	0.146
Discoid rash		-0.08	(-0.365,0.205)	0.579
Photosensitivity		-0.029	(-0.159,0.1)	0.65
Oral/Nasal ulcer		-0.05	(-0.175,0.074)	0.428
Alopecia		0.096	(-0.039,0.233)	0.163
Livedo reticularis		-0.108	(-0.649,0.434)	0.696
Raynaud's		-0.025	(-0.194,0.144)	0.772
Dry eye/ mouth		-0.025	(-0.129,0.081)	0.650
Vasculitis		-0.035	(-0.251,0.181)	0.748
Musculoskeletal manifestations		0.244	(-0.096,0.584)	0.159
Arthralgia		-0.339	(-0.657,-0.022)	**0.036***
Arthritis		-0.162	(-0.29,-0.025)	**0.019***
Pulmonary manifestations		-0.338	(-0.388,0.655)	0.846
Pleurisy		0.133	(-0.388,0.655)	0.614
Pleural effusion		-0.338	(-0.378,0.310)	0.846
Cardiac manifestations		0.405	(-0.301,1.113)	0.259
Pericardial effusion		-0.188	(-0.892,0.515)	0.23
CAD		0.06	(-0.429,0.557)	0.797
Serositis		-0.18	(-0.669,0.334)	0.487
Neurological manifestations		0.07	(-0.12,0.285)	0.45
Hematological manifestations		-0.095	(-0.366,0.174)	0.486
Hemolytic anemia		0.006	(-0.234,0.246)	0.96

Leucopenia	-0.01	(–0.343,0.14)	0.408
Thrombocytopenia	-0.177	(–0.416,0.061)	0.144
APS Syndrome	0.004	(–0.207,0.216)	0.967
Obstetric complications	0.23	(0.011,0.449)	**0.039***
Arterial/ Venous thrombosis	-0.018	(–0.476,0.438)	0.935
Laboratory Features			
ESR	0.049	(–0.06,0.16)	0.376
Urea	0.177	(-0.091,0.445)	0.345
Serum albumin	-0.068	(–0.219,0.082)	0.372
C3	0.191	(0.024,0.357)	**0.024***
C4	0.122	(–0.043,0.288)	0.146
Immune Profile			
Anti-dsDNA	0.167	(0.018,0.315)	**0.028***
Anti RO	0.075	(–0.141,0.29)	0.489
Anti LA	0.195	(–0.087,0.478)	0.172
Total APL profile	-0.021	(–0.157,0.114)	0.755
SLEDAI Score			
Mild disease activity	-0.14	(-0.267,-0.018)	**0.025***
Moderate disease activity	0.067	(–0.099, 0.234)	0.425
Severe disease activity	0.329	(0.072, 0.587)	**0.012***

CAD: Coronary artery disease, APS: Antiphospholipid syndrome, SLEDAI: SLE Disease Activity Index, ESR: Erythrocyte sedimentation rate, C: Complement, Anti-dsDNA: anti-double stranded DNA.

*statistically significant difference $p<0.05$
**statistically highly significant difference $p<0.001$

Remission and Non-Remission Groups

LN group was divided into two groups: Remission group (n=128) (73.6%) and Non-Remission groups (n=46) (26.4%) based on achieving complete renal remission within 2 years from development of LN.

Relative risk was done in the current study to assess the risk factors associated with non-remitting LN, based on the data of **2nd** and **3rd stations**.

The presence of proliferative LN classes (III and IV) in renal biopsy carried 4 times higher risk for non-remitting LN and this was statistically significant **(RR=4) (CI=1.516- 10.554).** Moreover, the presence of fibrinoid necrosis carried two and half times higher risk for the non-remitting LN and this was statistically significant **(RR=2.272) (CI=1.136- 4.542).** 2ry APS carried 3 times higher risk for the non-remitting LN and this was statistically significant **(RR=2.965) (CI=1.591- 5.522).** At the 3rd station, recurrent infections and

pregnancy carried two and half times higher risk for the non-remitting LN and this was statistically significant **(RR=2.603, 2.222**) **(CI=1.518- 4.463, 1.216- 4.061)** respectively. The presence of constitutional manifestations carried **25.5** times higher risk for the non-remitting LN and this was statistically significant **(RR=25.259) (CI=6.32-100.948).** The presence of musculoskeletal manifestations carried two times higher risk for the non-remitting LN and this was statistically significant **(RR=1.741) (CI=1.07- 2.833)**. Moreover, pulmonary and **c**ardiac manifestations carried **two** and half times higher risk for the non-remitting LN and this was statistically significant **(RR=2.063, 2.358) (CI=1.231- 3.457, 1.101- 5.046)** respectively **(Table-3)**.

On the other hand, regularity on treatment was protective factor against non-remitting LN and this was statistically significant **(RR=0.183)(CI=0.122- 0.275) (Table-3).**

Table-3 : Relative risk for non-remitting LN.

Variables	RR	95% CI
Demographic Feature		
Sex	1.385	0.69- 2.781
SLE-LN interval	1.374	0.839- 2.249
2nd Station (At development of LN)		
Clinical Presentation of LN		
HTN	1.104	0.633- 1.735
Lower limb edema	1.0888	0.666- 1.832
Laboratory Features of LN		
Pyuria	1.309	0.736- 2.327
Hematuria	1.19	0.725- 1.953
Casts	0.9663	0.572- 1.622
Creatinine	1.520	0.845- 2.735
Urea	1.113	0.668-1.855
Serum albumin	1.207	0.681- 2.14
Anti-dsDNA	1.82	0.707- 4.679
RO	2.173	0.925- 5.106

LA	1.694	0.745- 3.851
APL	1.298	0.701- 2.402
C3	0.873	0.5- 1.524
C4	1.015	0.485- 2.122
Nephrotic range proteinuria	1.216	0.661- 2.237
Renal biopsy		
Proliferative LN Classes	**4**	**1.516- 10.554**
Active/ Chronic lesions	1.768	0.936- 3.34
Crescentic	1.510	0.723- 3.154
Fibrinoid necrosis	**2.272**	**1.136- 4.542**
TMA	1.536	0.509- 4.63
Associated disease manifestations		
Constitutional manifestations	1.11	0.59- 2.087
Mucocutaneous manifestations	0.924	0.531- 1.607
Vasculitis manifestations	0.745	0.21- 2.641
Musculoskeletal manifestations	0.916	0.543- 1.546
Pulmonary manifestations	0.762	0.334- 1.734
Cardiac manifestations	1.033	0.38- 2.8
Neurological manifestations	0.739	0.26- 2.1
Hematological manifestations	0.694	0.395- 1.218
APS manifestations	**2.965**	**1.591- 5.522**
SLEDAI Score		
SLEDAI	0.921	0.552-1.535
3rd Station		
Induction therapy	1	0.388- 2.184
Regularity on treatment	**0.183**	**0.122- 0.275**
Infections	**2.603**	**1.518- 4.463**

Pregnancy	**2.222**	**1.216- 4.061**
Associated disease manifestations		
Constitutional manifestations	**25.259**	**6.32- 100.948**
Mucocutaneous manifestations	1.512	0.857- 2.668
Vasculitis manifestations	1.536	0.509- 4.63
Musculoskeletal manifestations	**1.741**	**1.07- 2.833**
Pulmonary manifestations	**2.063**	**1.231- 3.457**
Cardiac manifestations	**2.358**	**1.101- 5.046**
Neurological manifestations	1.746	0.803- 3.792
Hematological manifestations	1.384	0.761- 2.516
APS manifestations	1.953	0.842- 4.528

SLE: systemic lupus erythematosus, LN: lupus nephritis, HTN: hypertension, Anti-dsDNA: anti-double stranded deoxyribonucleic acid, APL: antiphospholipid antibodies, C: complement, TMA: thrombotic microangiopathy,APS: antiphospholipid syndrome, SLEDAI: SLE disease activity index.
RR: relative risk, CI: confidence interval.
RR=1 means that event is equally likely in both groups, RR>1 means that event is more likely in LN group and RR <1 means that event is less likely in LN group.

As regards the predictors of non-remitting LN, the presence of each of: Active with chronic and chronic lesions in renal biopsy in 2nd station and recurrent infections, pregnancy and constitutional manifestations in 3rd station were predictors of non-remitting LN **(P=0.001**, **0.000, 0.035**, **0.000**) respectively. On the other hand, regularity on treatment was the only significant predictor of remission **(P=0.000) (Table-4)**.

Table-4 : Predictors for non-remitting LN.

Variables	B Coefficient	95% CI	P- value
Demographic Feature			
Age of onset	0.023	(-0.167,0.215)	0.806
Sex	0.123	(-0.122,0.368)	0.322

SLE-LN interval	0.077	(-0.155,0.311)	0.511
2nd Station (At development of LN)			
Clinical Presentation of LN			
HTN	0.004	(-0.151,0.16)	0.951
Lower limb edema	0.008	(-0.155,0.172)	0.918
Laboratory Features of LN			
Pyuria	0.052	(-0.112,0.218)	0.529
Hematuria	0.022	(-0.147,0.192)	0.79
Casts	0.004	(-0.152,0.16)	0.96
Creatinine	0.103	(-0.132,0.337)	0.388
Urea	-0.013	(-0.194,0.167)	0.885
Serum albumin	0.023	(-0.151,0.198)	0.793
Anti-dsDNA	0.126	(-0.06,0.313)	0.183
RO	0.235	(-0.017,0.487)	0.0671
LA	0.186	(-0.13,0.503)	0.243
APL	0.074	(-0.083,0.232)	0.351
C3	-0.123	(-0.329,0.081)	0.234
C4	0.098	(-0.068,0.265)	0.244
Nephrotic range proteinuria	0.0285	(-0.169,0.226)	0.775
Renal biopsy			
Proliferative LN Classes	0.071	(-0.053,0.195)	0.259
Active/ Chronic lesions	0.0921	(-0.0393,0.144)	**0.001****
Crescentic	0.046	(-0.199,0.291)	0.712
Fibrinoid necrosis	0.216	(-0.113,0.546)	0.197
TMA	0.125	(-0.26,0.512)	0.521
Associated disease manifestations			
Constitutional manifestations	0.032	(-0.14,0.203)	0.714

Mucocutaneous manifestations	-0.051	(-0.202,0.101)	0.511
Vasculitis manifestations	-0.054	(-0.351,0.243)	0.722
Musculoskeletal manifestations	-0.019	(-0.165,0.128)	0.803
Pulmonary manifestations	-0.075	(-0.281,0.13)	0.47
Cardiac manifestations	0.021	(-0.884,0.265)	0.884
Neurological manifestations	-0.093	(-0.347,0.162)	0.474
Hematological manifestations	-0.097	(-0.241,0.045)	0.18
APS syndrome	0.201	(-0.014,0.416)	0.067
SLEDAI Score			
Moderate disease activity	-0.022	(-0.161, 0.117)	0.754
Severe disease activity	0.022	(-0.117, 0.161)	0.754
3rd Station			
Induction therapy	0.001	(-0.06,0.062)	0.975
Regularity on treatment	-0.561	(-0.709,-0.412)	**0.000****
Infections	0.248	(0.12,0.376)	**0.000****
Pregnancy	0.23	(-0.016,0.444)	**0.035***
Associated disease manifestations			
Constitutional manifestations	0.524	(0.4,0.647)	**0.000****
Mucocutaneous manifestations	-0.007	(-0.164,0.149)	0.929
Vasculitis manifestations	-0.115	(-0.457,0.228)	0.508
Musculoskeletal manifestations	-0.0343	(-0.161,0.092)	0.592
Pulmonary manifestations	0.083	(-0.082,0.249)	0.319
Cardiac manifestations	0.268	(-0.057,0.595)	0.106
Neurological manifestations	0.189	(-0.108,0.488)	0.211
Hematological manifestations	0.096	(-0.089,0.282)	0.308
APS manifestations	0.244	(-0.11,0.606)	0.185

SLE: systemic lupus erythematosus, LN: lupus nephritis, HTN: hypertension, Anti-dsDNA: anti-double stranded deoxyribonucleic acid, APL: antiphospholipid antibodies, C: complement, TMA: thrombotic microangiopathy, APS: antiphospholipid syndrome, SLEDAI: SLE disease activity index.
*statistically significant difference $p<0.05$.
**statistically highly significant difference $p<0.001$.

Discussion:

LN is one of the most common manifestations of SLE. It represents a major risk factor for morbidity and mortality **[8] .** Therefore the present study was carried out to evaluate the risk factors and predictors of the occurrence of LN in relation to different epidemiological, clinical, laboratory features and disease activity in a cohort of Egyptian SLE patients. In addition, the risk factors and predictors were assessed for non-remitting LN.

In the present study, **69.6%** of SLE patients developed LN. This goes in agreement with previous several studies that stated that the incidence of LN was (70%) **[9],** (50%)**[10] ,** (60%)**[11] ,** (60%)**[12]** and (60.6%) **[13].**

However**,** lower incidence was reported in some previous studies that stated that the incidence of LN was (13.3%) in Korean cohort **[3] and** (**18.3%)** in Thai cohort **[14].** This may be due to different ethnicity and shorter duration of follow up as **Satirapoj** and his colleagues in **2007** retrospectively studied the 109 Thai patients who were diagnosed SLE during the period from 2001 to 2005.

As regard the risk factors of the development of LN, each of: juvenile onset SLE, the presence of constitutional and cardiac manifestations especially pericardial effusion and coronary artery disease carried one and half times higher risk in SLE patients to develop LN and this was statistically significant **(RR=1.26, 1.29, 1.36, 1.34, 1.44) (CI=1.062- 1.497, 1.067-1.568, 1.149- 1.612, 1.105- 1.62, 1.329- 1.569)** respectively**.** The explanation of the significant relative risk of cardiac manifestations in the form of pericardial effusion and coronary artery disease may be explained by the inflammation of serosal membranes (pleura, pericardium and peritoneum) and cardiovascular system in SLE is an immune-complex and complement-mediated pathway like glomerulonephritis**[15].**

This goes with several previous studies, which found that juvenile onset SLE was a risk factor for LN development **[7, 11, 16]**. In addition, many studies documented that young age was as a risk factors for LN development **[3, 17, 18].**

In the concordance with our finding**, Maldonado-Romero** and his associates in their study in Spain in 2016, found that fever and serositis were risk factors for LN development **[19].** Also, another previous study conducted by **Bastian** and his colleagues found that pleurisy was a risk factors for LN development in multiethnic cohort in USA in 2002**[20]**.

As regard the serological and immunological risk factors for LN development in the current work we found that hypocomplementemia (C3 and C4) carried one and half times higher risk for the development of LN and this was statistically significant **(RR=1.48, 1.44) (CI=1.24-1.785, 1.219-1.7)** respectively**.** Interestingly, positive anti-dsDNA antibodies carried 3 times higher risk for the development of LN and this was statistically significant **(RR=3.125) (CI=2.189-4.461).**

This goes in agreement with several previous studies, that stated that hypocomplementemia (C3 and C4) and anti-dsDNA antibodies were risk factors for LN development **[3, 5, 19].** Anti-dsDNA antibodies had a crucial role in the pathogenesis of LN, as LN is initiated by the deposition of anti-dsDNA antibodies containing ICs in the renal parenchyma, resulting in immune-mediated renal injury **[9].**

On the other hand, in the present study, the presence of each of: mucocutaneous and musculoskeletal manifestations in the form of arthralgia and arthritis and hematological manifestations especially leucopenia were protective factors against the development of LN and this was statistically significant **(RR=0.73, 0.82, 0.77, 0.779, 0.78**, **0.749**) **(CI= 0.633-0.842, 0.678-0.991, 0.657- 0.903, 0.667- 0.908, 0.631- 0.965, 0.564- 0.993)** respectively.

This goes with several previous studies, which found that chronic cutaneous lupus erythematosus was a protective factor against LN **[19, 21].** Moreover, another study done by **Sule** and his associates in **2015** found that malar rash was protective against LN **[22].**

On the contrary to our finding**, Maldonado-Romero** and his colleagues in **2016** retrospectively studied 30 patients with LN and 61 SLE patients without LN in Spain from 2000 to 2015, found that malar rash and oral ulcer were risk factors of LN **[19]. Also, Kwon** and his associates in **2018** did not find mucocutaneous manifestation as a risk factor for LN in the 37 Korean LN patients **[3]**. This may be due to small number of LN patients group or may be related to different ethnicity in both previous studies.

Unlike our results, some studies found that hematological manifestations were risk factors for LN development **[19, 23].**This may be due to small number of LN patients enrolled in the both previous studies and short study follow up period in the study done by **Burling and his colleagues.** Some previous studies, did

not find that hematological manifestations **[3, 22]** and musculoskeletal manifestations as a risk for LN development **[3].**

As regards the predictors of LN, juvenile onset SLE, constitutional manifestations, obstetric complications (mainly in the form of recurrent abortion), hypocomplementemia (C3), anti-dsDNA antibodies and severe disease activity were significant predictors for the development of LN **(P=0.041, 0.03, 0.039, 0.024, 0.028, 0.012)** respectively.

This goes in agreement with several previous studies, that found that anti-dsDNA antibodies**[3, 19, 20, 22],** hypocomplementemia (C3) **[3, 19, 24]** and severe disease activity were predictor for the development of LN **[20].**

On the contrary to the previous studies, in a study done by **Sule** and his colleagues in USA in **2015** on 47 patients with age ≤19 years at the onset of SLE, they did not find hypocomplementemia (C3 and C4) and severity of disease activity as predictors for the development of LN **[22].** This may be explained by juvenile age and small number of patients.

On the contrary**,** anaemia was a predictor for LN development by some other studies **[14, 23].** This may be explained by small number of LN patients and short study follow up period in the both studies.

In the present study, Adult onset SLE, mucocutaneous manifestations, arthralgia, arthritis and mild disease activity were protective factors against the development LN **(P=0.041, 0.001, 0.036, 0.019, 0.025)** respectively.

In the concordance with our finding, the presence of malar rash was protective against LN development **[22].** Moreover, discoid lupus erythematosus was a protective factor against LN development **[21, 25].**

On the contrary**, Kwon** and his colleagues in **2018** did not find mucocutaneous and musculoskeletal manifestations as predictors for LN development **[3].**

This may be due to different ethnicity, genetic predisposition, disease duration, duration of follow up of SLE patients, number of the studied SLE patients, response to different triggering mechanisms and different individual environments or cultural effects may be involved.

In the current study, **128 (73.6%)** of LN patients achieved complete renal remission (Remission group) while **46 (26.4%)** patients did not achieve complete renal remission after 2 years (Non-Remission group).

Our results did not match previous works who studied the incidence of complete renal remission, these studies had either lower or higher incidence. As **Davidson** and his colleagues **in 2018** retrospectively studied 176 lupus patients with biopsy-proven LN (III, IV and V), documented that 59.1% of patients achieved a complete renal remission by 2 years **[26].** In **2014**, a retrospective study conducted by **Touma** and his associates on 212 patients of Toronto Lupus cohort followed from 1970 until 2011 in Canada, reported that 52% of the LN patients achieved complete renal remission within 2 years **[27].**

On the other hand, **Luís and his associates in 2021** retrospectively studied 114 patients with a biopsy-proven proliferative LN (class III/IV), enrolled in two tertiary care European centers and found that most patients (91.7%) reached complete renal remission within one year **[12].**

RR was done in the current study using **95%** confidence interval, based on the data in the **2nd station** and **3rd stations** to detect the risk factors of non-remitting LN and found that the relative risk of non-remitting LN associated significantly with each of: the presence of proliferative LN classes (III and IV) in renal biopsy carried 4 times higher risk for non-remitting LN and this was statistically significant **(RR=4) (CI=1.516- 10.554),** the presence of fibrinoid necrosis in renal biopsy carried two and half times higher risk for non-remitting LN and this was statistically significant **(RR=2.272) (CI=1.136- 4.542)** and the presence of 2ry APS carried 3 times higher risk for non-remitting LN and this was statistically significant **(RR=2.965) (CI=1.591- 5.522).**

In the concordance with our findings, **Gasparotto and his associates** in their study in **2020** found that proliferative LN classes carried higher risk for progressive renal disease **[28].** Also, **Dall'era and his colleagues in 2015** reported that mixed proliferative LN classes were risk factors for non-remitting LN **[29].** Non of previous works studied the presence of APS as a risk factor for non-remitting LN.

In the current study at the **3rd station**, we found that the relative risk of non-remitting LN associated significantly with each of: recurrent infections and pregnancy carried two and half times higher risk for non-remitting LN and this were statistically significant **(RR=2.603, 2.222**) **(CI=1.518- 4.463, 1.216- 4.061)** respectively, the presence of constitutional manifestations carried **25.5** times higher risk for non-remitting LN and this was statistically significant **(RR=25.259) (CI=6.32-100.948),** the presence of musculoskeletal manifestations carried **two** times higher risk for non-remitting LN and this was statistically significant

(RR=1.741) (CI=1.07- 2.833) and the presence of pulmonary and **c**ardiac manifestations carried **two** and half times higher risk for non-remitting LN and this were statistically significant **(RR=2.063, 2.358) (CI=1.231- 3.457, 1.101- 5.046)**.

This goes in agreement with several previous studies, that stated that pregnancy **[16, 30, 31]** and infections **[32, 33]** carried greater risk of renal disease progression**.**

Interestingly, the only protective factors from non-remitting LN was regularity on treatment and this was statistically significant **(RR=0.183)(CI=0.122- 0.275).**

In the concordance with our findings, several studies supported that lower adherence to treatment was associated with greater risks of renal disease progression **[28, 34]**.

As regards the predictors of non-remitting LN, multivariate logistic regression analysis was done to determine the significant predictors for non-remitting LN in the studied LN patients group, based on the data in the **2nd and 3rd stations**.

In the current study, the presence of active with chronic or chronic lesions in renal biopsy, recurrent infections, pregnancy and constitutional manifestations were predictors for non-remitting LN **(P=0.001**, **0.000, 0.035**, **0.000**) respectively. However, regularity on treatment was the only predictor of remission **(P=0.000)**.

These findings go with the study done by **Almalki and his colleagues in 2019,** who documented that histological activity/chronicity pattern was found to be a significant predictor for remission, as patients with active lesions more likely to achieve complete renal remission than active/chronic and chronic lesions**[35]**.

In the concordance with our findings, several studies reported that no isolated urinary finding were predictors for LN remission, as proteinuria at time of LN development unable to predict the long-term kidney outcome **[29, 36-38]**.

However, in some previous studies, it was found that lower levels of proteinuria at the time of development of LN was considered as a predictor of remission **[12, 27]**. Also, some other studies found that higher SCr was considered as predictor poor renal outcome **[28, 39]**. This may be due to that the majority of the LN patients enrolled in our study had normal creatinine level and subnephrotic range proteinuria which may be due to thoroughly follow up of our SLE patients and early diagnosis of LN.

Conclusion

In conclusion, LN is aggressive part of SLE disease and most studies that dealed with LN were cross sectional biased studies. Relative risk and predictors were rarely done due to long follow up period despite that they are more accurate and gives better idea about the disease.

We did a retrospective follow up study to assess the relative risk and predictors of LN in a cohort of Egyptian systemic lupus patients. We reported that, juvenile onset SLE, constitutional and cardiac manifestations especially pericardial effusion and coronary artery disease, hypocomplementemia (C3 and C4) and positive anti-dsDNA antibodies were significant RR to the development of LN**,** while mucocutaneous and musculoskeletal manifestations in the form of arthralgia and arthritis and hematological manifestations especially leucopenia were significant protectors against the development of LN.

Among the predictors of LN, juvenile onset SLE, constitutional manifestations, obstetric complications, hypocomplementemia (C3), anti-dsDNA antibodies and severe disease activity were significant predictors for the development of LN, while adult onset SLE, mucocutaneous manifestations, arthralgia, arthritis and mild disease activity were protectors against the development LN

The significant RR for non-remitting LN were proliferative LN classes (III and IV) and fibrinoid necrosis in renal biopsy, 2ry APS, recurrent infections, pregnancy, constitutional, musculoskeletal, pulmonary and **c**ardiac manifestations.

Among the predictors of non-remitting LN, active with chronic or chronic lesions in renal biopsy, recurrent infections, pregnancy and constitutional manifestations were significant predictors for non-remitting LN**,** while regularity on treatment was the only significant protector against non-remitting LN.

The present study has some limitations as: considerable low number of patients, it is a one center study, study design was mainly retrospective with a lot of changes that already developed in the diagnostic criteria, activity scores and management lines. A further study is required with multicenter approach in Egyptian Rheumatology practice with larger number of patients and more investigators in a prospective larger study.

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