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Original article

Cognitive Function Disorders in Adult Patients with Lupus Nephritis and its Correlation with the Disease Activity

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Abstract

Background: A complex autoimmune disease, systemic lupus erythematosus (SLE) mostly strikes females. The abnormal accumulation of immune complexes, the involvement of numerous organs, and the excessive production of different types of autoantibodies are the hallmarks of this condition. **The purpose of this study** is cognitive function disorders in adult patients with lupus nephritis (LN) and their correlation with the disease activity of LN, as compared to SLE without nephritis. **Methods:** This case-controlled study included 120 patients who carried out at the Nephrology Unit, Internal Medicine Department, at Benha University Hospitals from April 2022 to April 2024. Patients were divided into two groups: Group 1: Fifty adult patients with SLE who fulfill the criteria of American College of Rheumatology, Group 2: Seventy adult patients with LN. **Results**: The estimated glomerular filtration rate, complement component 3, and complement component 4 in the LN group all showed significant positive correlations with the Montreal Cognitive Assessment (MOCA) score. Otherwise, the following markers were found to be significantly inversely correlated with the MOCA score: systolic and diastolic blood pressure, urea and creatinine levels, total leukocyte count, erythrocyte sedimentation rate, C-reactive protein, antiphospholipid antibodies, lupus anticoagulant, protein/creatinine ratio, albumin/creatinine ratio, 24-hour urine protein, activity index, and chronicity index.

Conclusion: SLE patients frequently experience subclinical cognitive deficits that are not adequately assessed. The LN group reported significantly lower MOCA scores than the SLE group. MOCA is an instrument for detection of moderate cognitive impairment in LN, with a specificity of 86% and a sensitivity of 81.4%.

Keywords: Cognitive impairment, Disease activity, Disorders, Lupus nephritis.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder primarily impacts women. Some of its most notable features include the accumulation of immune complexes, the excessive production of a diverse array of autoantibodies, and the involvement of multiple organs. Inconsistent clinical courses and prognoses are the hallmarks of SLE. The formation of antigen-antibody complexes occurs as these auto-antibodies bind to their specific antigens. This results in the accumulation of these chemicals in various organs and tissues, including the circulatory system, the kidneys, the subcutaneous tissue, and the neurological system (1).

SLE's most prevalent and severe manifestation is kidney involvement, which affects up to 75% of patients throughout the disease's progression. Subclinical laboratory abnormalities, overt nephritis, nephrotic syndrome, and rapidly progressive renal failure are all possible manifestations of lupus nephritis (LN)(2).

Seizures and psychosis are hallmarks of SLE and affect multiple bodily systems and the brain. In addition, individuals diagnosed with SLE exhibit a wide range of neuropsychiatric symptoms. As a result of all these neurological symptoms, neuropsychiatric systemic lupus erythematosus is medically diagnosed. Problems with cognition, organic brain syndromes, convulsions, delirium, psychosis, and peripheral and central nervous system effects are all possible symptoms of neuropsychiatric systemic lupus erythematosus (NPSLE)(3).

When it comes to neurological and mental disorders, SLE can manifest in 19 different ways, one of which is cognitive dysfunction (CD), using standards set out by the ACR. This condition is present in 20 to 80 percent of individuals with SLE, which is twice the prevalence of the general population. Additionally, it is recognized as the most prevalent manifestation of the disease, with a prevalence of 55-80% in NPSLE patients (4). An impairment in any or all the cognitive domains, including reasoning, attention, executive skills, memory, visual-spatial processing, language, and psychomotor speed, is considered a significant impairment in SLE by the AC, regardless of the complexity or fundamentality of the impairment. Commonly impacted areas include learning, attention, and memory (5).

CD diagnosis in NPSLE is most reliably achieved through neurocognitive testing. Comprehensive traditional batteries or the Automated Neuropsychological Assessment Metric (ANAM) are the most frequently used assessment batteries for the evaluation of cognition in SLE. A psychologist or a psychometrist who has received specialized training frequently administers these batteries. There are

numerous additional assessments available, including the Hopkins Verbal Learning Test Revised, the Modified Mini-Mental State Exam (MMSE), the controlled oral word association test, and the Montreal Cognitive Assessment (MoCA) (6).

Montreal Cognitive Assessment (MOCA) was intended to detect the same domain as Modified Mini-Mental State Exam (MMSE); however, it is more comprehensive and incorporates the clock-drawing test and trail test (connecting point points). Scores of 26 or higher are considered normal, while the utmost point value of this assessment is 30. This assessment is accessible in 36 languages and dialects and lasts approximately 5-10 minutes. MoCA instruments with a threshold value of < 26/30 were employed to evaluate impaired cognitive function in SLE. The results indicated a 75% accuracy rate, 73% specificity, and a reasonable sensitivity of 83% (7).

The study's objectives were to compare cognitive function impairments in adults with lupus nephritis to those in systemic lupus erythematosus (SLE) patients without nephritis and to examine whether there is an association between the two.

Patients and methods

This case-controlled study included 120 patients who were admitted at the Nephrology Unit, Internal Medicine Department, at Benha University Hospitals between April 2022 and April 2024.

All participated patients received an explanation of the purpose of the study and had a secret code number. The patients gave their informed written permission. The study was Conducted after being approved by the Research Ethics Committee, Faculty of Medicine, and Benha University.

Inclusion criteria were estimated glomerular filtration rate (eGFR) > 30mL/min/1.73m2, age > 18 years. eGFR is determined using the CKD-EPI equation (8). GFR = 141 × min (Scr /κ, 1) α multiplied by the maximal value of Scr/κ, which is 1. Age × 1.018 [if female] × 1.159 [if black" In what location is -1.209 × 0.993 located? Mg/dL is the unit of measurement for serum creatinine (Scr). Values of κ and α are as follows: κ is 0.7 for females and 0.9 for males, while α is -0.329 for females and -0.411 for males. The "min" and "max" values represent the minimal and maximum Scr /κ values, respectively.

Exclusion criteria were cancer, structural and functional heart disease, pregnancy, liver cirrhosis, alcohol intake, severe profound intellectual disability, and central nervous system disease.

Grouping: Patients were divided into two groups: **Group 1:** Fifty adult patients with systemic lupus erythematosus who fulfill the criteria of

2019 EULAR/ACR (European League Against Rheumatism/ American College of Rheumatology) (positive ANA at least once as obligatory entry criterion; followed by additive weighted criteria grouped in 7 clinical (constitutional, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal) and 3 immunological (antiphospholipid antibodies, complement proteins, SLE-specific antibodies) domains, and weighted from 2 to 10. Patients accumulating ≥10 points are classified.) (9), **Group 2:** Seventy adult patients with Lupus Nephritis.

All studied cases were subjected to the following: **Demographic data collection from each patient including** [Age (years), gender, concomitant treatments e.g.: - (Steroid, Mycophenolate mofetil)]. Clinical examination including: [Blood pressure (BP), peripheral edema or periorbital edema, headache and dizziness, nausea and vomiting, malar rash, discoid rash, oral ulcers and arthritis, and coagulopathy (Deep vein thrombosis, cerebrovascular stork, ischemic heart disease], **Lab investigations including** [Blood urea nitrogen (BUN) testing, complete blood count (CBC), fasting blood glucose, Hemoglobin A1c level (HbA1c), serum creatinine assessment, urinalysis, spot urine test for albumin, protein: Protein /creatinine ratio (PCR), 24-hour urine test for protein excretion (24 hours albumin and protein) normal less than 150 mg per day, antibodies to double-stranded DNA (dsDNA) were assayed by indirect immunofluorescence (IIF) using crithidia luciliae as a substrate, antinuclear antibodies (ANA) were evaluated by an IIF technique using Hep-2 cells. Normal<1/80, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum troponin I, Anti-phospholipid antibodies (APL), lupus anticoagulant (LA), lactate dehydrogenase (LDH), and eGFR].

All patients of group 2 were subjected to kidney biopsy. Ultrasound-guided biopsy procedure was used which is fast, safe, and accurate in tissue sampling, Light microscopy and immunohistochemical staining were performed.

According to the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS) in 2003, the histopathological characteristics of LN were classified as follows: (10) Class I comprises minimal mesangial lupus nephritis, Class II comprises mesangial proliferative lupus nephritis, Class III comprises focal lupus nephritis (proliferative and sclerosing; active and chronic), Class IV comprises diffuse lupus nephritis (proliferative and sclerosing; segmental and global), Class V comprises membranous lupus nephritis, and Class VI comprises advanced sclerosis lupus nephritis. Conducting an evaluation of cognitive function through:

Montreal Cognitive Assessment (MoCA)

About ten minutes is required to administer the MoCA, a paper-and-

pencil tool with a 30-point scale. A large variety of cognitive abilities are assessed by the MoCA, such as focus, memory, abstraction, calculation, orientation, language, spatial reasoning, and executive functions. This item has been translated into 36 languages and dialects and is currently in widespread use on a global scale (11). MOCA score ranges between (0 and 30) a score of 26 or over is normal. All instructions may be repeated once (MoCA Version 7.1 ,2010). (12)

Alternating trail making: A participant receives one point for accurately drawing the following pattern without crossing lines: 1-A- 2-B- 3-C- 4-D- 5-E. Any mistake that is not self-corrected (i.e., fixed before moving on to the Cube challenge) gets a score of zero. In the event if the participant draws a straight line from point E to point A, they will not receive any points (1). (12)

Visuoconstructional skills (Cube): Drawings that are executed with precision are awarded a single point. Ensure that the cube's orientation in space is preserved and ensure that the drawing is three-dimensional. It is imperative that all lines be drawn and that they intersect with minimal or no space. There are no additional lines, and the lines must be relatively parallel and have similar lengths (rectangular prisms are permissible). No point is awarded for failure to meet any of the criteria. (12)

Visuoconstructional skills (Clock): The subsequent three criteria are each allocated a single point: (1) Contour with one point: Either a square or a circle must be used to depict the clock contour. 1) Numbers (1 point): All timepiece numbers must be listed without any additional numbers. To accurately represent the time, two palms must collaborate, subsequently earning one point. The clock face's numbers must be positioned in the correct order, erect, and within the approximate quadrants. The hour hand must be markedly shorter than the minute hand. (12)

Naming: One point is given for each of the following responses: (1) lion (2) rhinoceros or rhino (3) camel or dromedary. (12)

Memory: No points are given for trials one and two. (12)

Attention:

Backward digit span: For each sequence that is accurately repeated, one point is granted. Vigilance: A zero-to-one error is awarded one point for either tapping on the incorrect letter or failing to press on letter A. Series of sevens: Evaluation of this item is contingent upon a maximum of three points. For no correct subtractions, assign zero points. For one correct subtraction, assign one point. For two or three correct subtractions, assign two or three points. For four or five correct subtractions, assign three points. Subtractions are assessed independently; for instance, if

the subject inputs an incorrect number but subsequently subtracts 7 accurately, each corresponding correct subtraction is recorded. As an illustration, a subject may respond with "92 – 85 – 78 – 71 – 64," in which the "92" is inaccurate, but all subsequent numbers are accurately subtracted. If a single error were committed, the mission would receive a score of three. (12)

Sentence repetition: 1 point is awarded for each sentence that is accurately repeated. Repetitions must be precise. Monitor for omissions, substitutions/additions, grammar errors/altering plurals, and other types of errors. (12)

Verbal fluency: For every syllable that the subject manages to utter in under a minute, they will receive 1 point. Marks or the back of the test sheet is where the examiner writes down the subject's answers. (12)

Abstraction: The scores are limited to the final two pairings. Each correctly answered combination is awarded one point. The responses that follow are all permissible: All of the subsequent responses are unacceptable: (train-bicycle = means of transportation, means of travel; you take journeys in both; ruler-watch = measuring instruments; commonly used for measurement). Trains and bicycles are composed of wheels, while rulers and timepieces are composed of numerals. (12)

Delayed recall: One point is allocated for each word recalled freely without any cues. (12)

Orientation: Every item that is satisfactorily addressed is awarded one point. It is imperative that the date and location (particularly the name of the hospital, clinic, and office) are precise. There are no points awarded if the subject makes an error of one day in the date and day. (12)

Total Score: Calculate the sum of all sub scores that are assigned on the right-hand side. There is a maximum of 30 points, and one point is added for each subject that has been completed within the last 12 years of formal education. An ultimate cumulative score of 26 or higher is necessary to be considered normal. (12)

Approval code: MD 5-8-2021

Statistical analysis

The data that was fed into the computer was analyzed using IBM's application software, SPSS 25.0 (IBM Corp., 2017). Version 25.0 of the Statistical Package for the Social Sciences (SPSS) for Windows. In Armonk, New York, IBM Corp. It was demonstrated that the distribution was normal by using the Shapiro-Wilk test. Common metrics used to display the quantitative data include median, IQR, mean, standard deviation, and range (both minimum and maximum). Evaluation of the results was conducted at a significant level of 5%. The data was coded as either

quantitative or qualitative based on its percentage or count. To establish connections between a multitude of nominal (categorical) variables, the chi-square test is advantageous. A Student t-test was implemented to evaluate the two groups if the quantitative variables were normally distributed. Mann Whitney test was used to compare the two sets of data for quantitative variables that did not follow normal distributions. Quantitative diagnostic tests that classify patients into two groups can be better understood by constructing a ROC curve, which plots the results against each other. The strength of the relationships between the non-parametric variables was assessed using Spearman (rs) Correlations. For statistical purposes, a P value below 0.05 was deemed significant.

Results

Table 1. In Lupus Nephritis group shown that age and median (IQR) age was significantly higher compared to SLE group (p=0.035).While, insignificant difference was observed between the two studied groups regarding gender (p>0.05), there was significant difference between the two studied groups regarding treatment (p<0.001) as the dual therapy of Steroid +Plaquenil was used higher in SLE group while the triple therapy of Steroid+ Plaquenil+ Cyclophosphamide was used higher in Lupus Nephritis group, and on comparison of urine analysis between SLE and Lupus Nephritis groups; it showed significant difference between them (p<0.001) as Lupus Nephritis group had more positive protein, Red blood cells (RBCs), RBCs cast and granular cast in urine than SLE group.

Table 2. According to comparison of blood pressure and renal function tests: (blood urea, serum creatinine, Albumin/creatinine ratio (ACR), PCR and 24h urine protein) group there was significant elevation in Lupus Nephritis group compared to SLE (p<0.001), while**,** eGFR was significantly lower in Lupus Nephritis group compared to SLE group (p<0.001), and Platelet's count showed significant decline in Lupus Nephritis group compared to SLE group (p=0.003). In Lupus Nephritis group TLC was significantly little higher compared to SLE group (p=0.014). insignificant difference was observed between the two studied groups regarding hemoglobin (Hb) level (p>0.05)**.** Anti-dsDNA, ANA, ESR, CRP, troponin I, APL and LA showed significant elevation in Lupus Nephritis group compared to SLE group (p<0.001). While complement component3(C3) and complement component4 (C4) were significantly lower in Lupus Nephritis group compared to SLE group (p<0.001). In addition, HbA1c was significantly little higher in SLE group compared to Lupus Nephritis group (p<0.001).

Table 3 shows peripheral oedema, periorbital oedema and headache were significantly higher in Lupus Nephritis group compared to SLE group (p<0.001,

p<0.001 & p<0.001 respectively). Otherwise, insignificant difference was found between the two groups regarding other manifestations (p>0.05), in Lupus Nephritis group, 30 (42.9%) cases had Lupus Glomerulonephritis class IV. The median (IQR) Activity index was 23 (20- 25) while the median (IQR) of chronicity index was 1 (0- 3).

MOCA score was significantly lower in Lupus Nephritis group compared to SLE group (p<0.001), there was a significant difference in cognitive impairment prevalence between SLE without nephritis and in lupus nephritis. In the SLE group, 14% of patients exhibited cognitive impairment, whereas 81.4% of those in the Lupus Nephritis group did (p<0.001) suggest a strong association between cognitive impairment and Lupus nephritis. The MOCA scores show a significant difference between the different lupus nephritis classes and SLE without nephritis (p< 0.001). SLE without nephritis had the highest cognitive function (26.96 ± 1.31), whereas lupus nephritis class IV showed the lowest scores (19.37± 3.43), indicating severe cognitive impairment. Pairwise comparisons revealed that class IV had significantly lower scores than class I (p= 0.010), highlighting the impact of severe nephritis on cognitive decline. However, no significant differences were observed between class I and SLE without nephritis (p= 0.852) or between class I and class II (p= 0.241) or between class I and class III (p= 0.110). **Table 4**

In SLE group, it was found that there was significant positive correlation between MOCA score with Hb (r=0.399, p=0.005), and C3 (r=0.462, p=0.001) while a significant negative correlation was found between MOCA score with ANA (r=-0.400, p=0.004), ESR (r=-0.345, p=0.014) and APL (r=-0.370, p=0.008). **Table 5**

The ROC curve showed that: MOCA is a valuable tool for detecting cognitive impairment in lupus nephritis with 81.4% sensitivity and 86% specificity. The positive predictive value (PPV) is 89.1% and its negative predictive value. (NPV) is 76.8% (AUC= 0.938 & p <0.001). **Figure 1**

Table 1: Demographic characteristics, treatment of SLE and urine analysis finding without nephritis and lupus nephritis.

		Group (1) SLE group (N= 50)		Group (2) Lupus Nephritis group (N= 70)		Test value	P-value
		No.	**%**	**No.**	**%**		
Gender	**Male**	5	10.0%	7	10.0%	X^2= 0.00	>0.999
	Female	45	90.0%	63	90.0%		
Age (years)	**Median (IQR)**	24.5 (21- 28)		25.5 (22- 33)		Z_{MWU} = 2.107	**0.035***
	Mean± SD	24.88± 4.65		27.59± 6.53			
	Range	19 - 37		19 - 43			
		Treatment					
Steroid /Plaquenil		33	66.0%	6	8.6%	X^2= 62.77	**<0.001****
Steroid /Plaquenil / Cyclophosphamide		0	0.0%	32	45.7%		
Steroid /Plaquenil / MMF		11	22.0%	22	31.4%		
Steroid/Plaquenil /Azathioprine		6	12.0%	2	2.9%		
Steroid /Plaquenil /Cyclosporine		0	0.0%	8	11.4%		
		Urine analysis					
Normal		40	80.0%	4	5.7%	X^2= 57.27	**<0.001****
Abnormal		10	20.0%	66	94.3%		
▪ **Protein +**		10	20.0%	30	42.9%	X^2= 74.2	**<0.001****
▪ **Protein ++**		0	0.0%	24	34.3%		
▪ **Protein +++**		0	0.0%	12	17.1%		
▪ **RBCs +++**		0	0.0%	22	31.4%	X^2= 32.5	**<0.001****
▪ **RBCs cast**		0	0.0%	11	15.7%		
▪ **Granular cast**		0	0.0%	12	17.1%	X^2= 7.71	**0.005****

SLE: Systemic lupus erythematosus, MMF: Mycophenolate mofetil, P value >0.05: Not significant, *P value <0.05 is significant, **p<0.01 is highly significant. SD: standard deviation, X2: Chi- Square test, ZMWU: Mann-Whitney U Test

Table 2: Blood pressure, renal function tests, CBC, and laboratory findings in SLE without nephritis and in lupus nephritis

	Group (1) SLE group (N= 50)			Group (2) Lupus Nephritis group (N= 70)			Mann-Whitney U test	
	Median	IQR		Median	IQR		Z_{MWU}	P-value
SBP (mm/Hg)	110.0	110.0	120.0	150.0	125.0	170.0	7.157	**<0.001****
DBP (mm/Hg)	80.0	80.0	80.0	90.0	80.0	95.0	7.282	**<0.001****
Renal function tests								
Urea (mg/dl)	25.0	22.0	33.0	70.0	35.0	90.0	6.967	**<0.001****
Creatinine (mg/dl)	0.8	0.6	0.9	1.5	1.0	1.8	6.465	**<0.001****
ACR (g/mmol)	140.0	105.0	175.0	1680	1256	2660	9.319	**<0.001****
PCR (mg/mg)	0.315	0.28	0.43	2.25	1.70	3.50	9.317	**<0.001****
24h urine protein (mg/24h)	200.0	140.0	250.0	2300	1700	3500	9.327	**<0.001****
eGFR(ml/min/ 1.73m2)	113.8	87.9	126.0	52.1	39.9	77.8	6.503	**<0.001****
Hb (g/dL)	10.0	8.8	10.1	9.0	8.8	10.0	1.513	0.130
Platelets ($\times10^9$/L)	350	250	400	300	200	350	2.927	**0.003****
TLC ($\times10^9$/L)	6	4.6	6.9	6.5	5.55	7.5	2.466	**0.014***
Laboratory findings								
Anti-dsDNA	1/160	1/140	1/180.0	1/200	1/180	1/220	5.956	**<0.001****
ANA	1/160	1/140	1/180.0	1/200	1/170	1/220	6.058	**<0.001****
ESR (mm/hr)	40.0	35.0	50.0	85.0	75.0	90.0	9.221	**<0.001****
CRP (mg/L)	15.0	10.0	20.0	35.0	30.0	55.0	8.516	**<0.001****
Troponin I (ng/ml)	0.003	0.002	0.005	0.015	0.006	0.021	6.714	**<0.001****
APL (unit/ml)	12.0	11.0	15.0	19.5	15.0	25.0	6.741	**<0.001****
LA (second))	33.0	31.0	35.0	42.0	35.0	48.0	5.485	**<0.001****
LDH(U/L.)	190.0	160.0	220.0	190.0	170.0	210.0	0.396	0.692
FBS (mg/dl)	96.0	88.0	100.0	100.0	90.0	103.0	1.685	0.092
HbA1c (%)	5.4	5.3	5.6	5.1	4.8	5.3	5.169	**<0.001****
C3(mg/dL)	100.0	90.0	110.0	75.0	59.0	85.0	8.296	**<0.001****
C4(mg/dL)	24.0	20.0	30.0	8.0	4.0	9.0	8.027	**<0.001****

SLE: Systemic lupus erythematosus, SBP: systolic blood pressure, DBP: diastolic blood pressure, ACR: Urine albumin to creatinine ratio, PCR: Protein /creatinine ratio, , eGFR: Estimated Glomerular Filtration Rate, Hb: hemoglobin, TLC: total leukocyte count, ANA: Antinuclear Antibody, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, APL: Antiphospholipid Antibodies, LA: Lupus anticoagulant, LDH: Lactate dehydrogenase, FBS: Fasting blood sugar, HbA1c: glycated hemoglobin, C: complement component, SD: standard deviation, IQR: Interquartile range, ZMWU: Mann-Whitney U Test, P value >0.05: Not significant, *P value <0.05 is significant, **p<0.01 is highly significant.

Table 3: Clinical manifestations of SLE without nephritis and lupus nephritis and histopathologic classification of lupus nephritis according to ISN/RPS 2003

		Group (1) SLE group (N= 50)		Group (2) Lupus Nephritis group (N= 70)		Chi- Square test	
		No.	**%**	**No.**	**%**	X^2	**P-value**
Peripheral oedema		0	0.0%	52	74.3%	65.546	**<0.001****
Periorbital oedema		0	0.0%	20	28.6%	17.143	**<0.001****
Headache		7	14.0%	38	54.3%	20.197	**<0.001****
Dizziness		0	0.0%	0	0.0%	-	-
Nausea and vomiting		7	14.0%	18	25.7%	2.427	0.119
Malar rash		23	46.0%	36	51.4%	0.344	0.558
Discoid rash		3	6.0%	2	2.9%	0.721	0.396
Oral ulcers		36	72.0%	41	58.6%	2.287	0.130
Arthritis		32	64.0%	36	51.4%	1.877	0.171
Coagulopathy	**DVT**	3	6.0%	8	11.4%	1.032	0.357^{FET}
Histopathologic classification of Lupus Nephritis according to ISN/RPS 2003.						**Group (2) Lupus Nephritis group (N= 70)**	
Class	**Class I (Minimal mesangial lupus nephritis)**					2 (2.9%)	
	Class II (Mesangial proliferative lupus nephritis)					6 (8.6%)	
	Class III (Focal lupus nephritis)					20 (28.6%)	
	Class IV (Diffuse lupus nephritis)					30 (42.9%)	
	Class V (lupus Membranous nephritis)					12 (17.1%)	
Activity index	**Median (IQR)**					6 (2- 10)	
	Mean± SD					5.80± 4.08	
	Range					1 – 12	
Chronicity index	**Median (IQR)**					1 (0- 3)	
	Mean± SD					1.43± 1.40	
	Range					0 – 5	

SLE: Systemic lupus erythematosus, P value >0.05: Not significant, *P value <0.05 is significant, **p<0.01 is highly significant. FET: Fischer exact test, X2: Chi- Square test

Table 4: Montreal cognitive assessment (MOCA), percentage of cognitive impairment in SLE without nephritis and in lupus nephritis and MOCA in lupus nephritis according to the histopathological classification

			Group (1) SLE group (N= 50)		Group (2) Lupus Nephritis group (N= 70)		Test value	P-value
MOCA score	**Median (IQR)**		27 (26- 28)		23 (20- 25)		Z_{MWU} =	**<0.001****
	Mean± SD		26.96± 1.31		22.10± 3.5		8.219	
	Range		25 – 30		15 – 27			
Cognitive impairment			7	14.0%	57	81.4%	X2= 53.28	**<0.001****
MOCA in lupus nephritis								
	SLE without nephritis	**Lupus nephritis class I**	**Lupus nephritis class II**	**Lupus nephritis class III**	**Lupus nephritis class IV**	**Lupus nephritis class V**	**Kruskal Wallis test**	
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Mean ±SD**	**Kw**	**P-value**
MOCA score	26.96 ±1.31	26.50 ±0.71	24.67 ±0.82	23.6 ±1.93	19.37 ±3.43	24.50 ±1.17	82.4	**<0.001****
Pairwise comparison	Lupus nephritis class I vs SLE without nephritis	**---**	Lupus nephritis class I vs Lupus nephritis class II	Lupus nephritis class I vs Lupus nephritis class III	Lupus nephritis class I vs Lupus nephritis class IV	Lupus nephritis class I vs Lupus nephritis class V	----	**---**

MOCA: Montreal Cognitive Assessment, SLE: Systemic lupus erythematosus, P value >0.05: Not significant, *P value <0.05 is significant, **p<0.01 is highly significant. X2: Chi- Square test, ZMWU: Mann-Whitney U Test

Table 5: Correlation between MOCA score with different parameters in SLE without nephritis and in lupus nephritis, using Spearman Correlation coefficient.

	MOCA score			
	SLE group		Lupus Nephritis group	
	ρ	p- value	ρ	p- value
Age / years	-0.215	0.134	-0.130	0.282
SBP (mm/Hg)	-0.233	0.104	-0.316	**0.008****
DBP (mm/Hg)	-0.180	0.212	-0.313	**0.008****
Urea (mg/dl)	-0.074	0.610	-0.411	**<0.001****
S. Creatinine(mg/dl)	-0.157	0.275	-0.450	**<0.001****
FBG (mg/dl)	0.146	0.311	-0.266	**0.026***
HbA1C (%)	0.247	0.084	0.018	0.879
Hb (g/dL)	0.399	**0.005****	0.089	0.462
Platelets count ($\times 10^9$/L)	-0.133	0.356	0.126	0.300
TLC ($\times 10^9$/L)	0.132	0.362	-0.257	**0.034***
ACR(g/mmol)	-0.670	0.815	-0.670	**<0.001****
PCR (mg/mg)	-0.664	0.522	-0.664	**<0.001****
24h urine protein (mg/24h)	-0.670	0.703	-0.670	**<0.001****
Anti-dsDNA	0.077	0.596	0.001	0.993
ANA	-0.400	**0.004****	-0.046	0.704
ESR (mm/hr)	-0.345	**0.014***	-0.705	**<0.001****
CRP (mg/L)	-0.006	0.967	-0.764	**<0.001****
S. Troponin I(ng/ml)	-0.039	0.786	-0.172	0.160
APL (unit/ml)	-0.370	**0.008****	-0.598	**<0.001****
LA (second))	-0.286	0.044	-0.593	**<0.001****
LDH(U/l)	-0.193	0.179	0.067	0.580
eGFR(ml/min/1.73m2)	0.165	0.252	0.509	**<0.001****
C3(mg/dl)	0.462	**0.001****	0.560	**<0.001****
C4(mg/dl)	0.260	0.069	0.675	**<0.001****
Activity index	.	.	-0.883	**<0.001****
Chronicity index			-0.474	**<0.001****

SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, HbA1C: glycated hemoglobin, Hb: hemoglobin, TLC: total leukocyte count, ACR: Urine albumin to creatinine ratio, PCR: Protein /creatinine ratio, ANA: Antinuclear Antibody, ESR: Erythrocyte Sedimentation Rate , CRP: C-Reactive Protein, APL: Antiphospholipid Antibodies, LA: Lupus anticoagulant, LDH: Lactate dehydrogenase, eGFR: Estimated Glomerular Filtration Rate, C: complement component, P value≤ 0.05 is significant; P value> 0.05 is not significant, r: Spearman correlation,

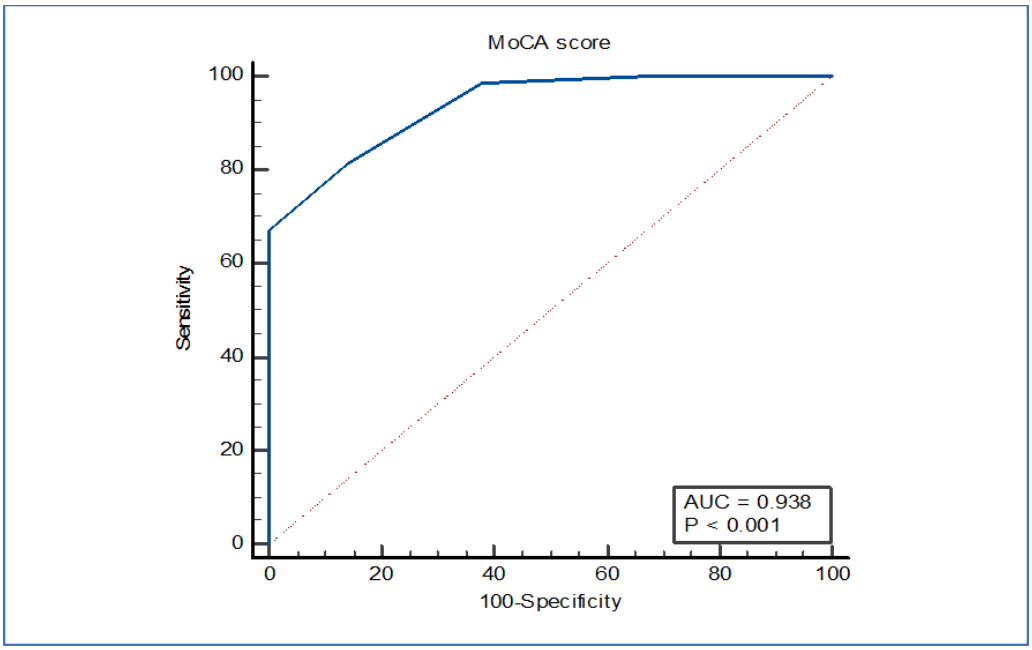

Figure 1: The sensitivity and specificity of MOCA score

Discussion

The dual therapy of steroids and plaquenil was used more frequently in the SLE group, whereas the triple therapy of steroids, plaquenil, and cyclophosphamide was used more frequently in the Lupus Nephritis group, demonstrating a significant difference between the two investigated groups regarding treatment.

In agreement with Kosałka et al, (13) who revealed that in both SLE subgroups, corticosteroids were the most common therapy regimen, although as expected, LN patients were more frequently treated with immunosuppressants such as azathioprine, mycophenolate mofetil, cyclophosphamide, and rituximab

The current study revealed significant elevation of systolic and diastolic blood pressure (DBP) in Lupus Nephritis group compared to SLE group.

In consistency with the current study, Kosałka et al., (14) in their study observed a higher prevalence of arterial hypertension and hypercholesterolemia in LN, which were associated with an increased mortality rate and End-Stage Kidney Disease (ESKD) in LN with no significant differences in diabetes mellitus, heart failure, atrial fibrillation, malignant tumors, peripheral artery disease, myocardial infarct, ischemic stroke, and venous thromboembolism between the analyzed LN and non-LN patients.

The current study found that among the SLE group, oral ulcers were the most common presenting symptom at 72%, followed by arthritis at 64%, and malar rash at 46%. Oral ulcers were reported by 58.6% of patients with Lupus Nephritis, peripheral edema by 74.3%, and headache by 54.3%. Significantly more people with Lupus Nephritis had peripheral edema, periorbital edema, and headache than people with SLE.

Hanly et al., (15) found that non-LN patients were characterized by a higher presence of mucocutaneous manifestations, photosensitivity, and Raynaud's phenomenon with a higher prevalence of joint involvement. These observations are in line with the current study. While Kosałka et al.,(14) analyzed SLE clinical characteristics in LN early and late onset subgroups. Interestingly, they documented that the delayed-onset LN had more severe clinical manifestations other than kidney involvement, including hematological signs (97.56%), joint inflammation (91.87%), and constitutional symptoms (86.18%). Early-onset lupus nephritis (LN) patients exhibited similar predominant symptoms, but joint involvement was less frequent in this LN group, with corresponding percentages of 93.75%, 79.81%, and 77.88%, respectively, for the three manifestations. Furthermore, delayed-onset LN patients had more common other clinical SLE manifestations, such as mucocutaneous, lymphadenopathy, Raynaud's phenomenon and myalgia.

In the current study, Lupus Nephritis group had significantly higher levels of serum creatinine, ACR, PCR, and 24-hour urine protein compared to the SLE group. The renal function of the two groups differs statistically ($P<0.001$). While eGFR was significantly lower in Lupus Nephritis group compared to SLE group ($p<0.001$).

Additionally, when contrasted with the SLE group, the Lupus Nephritis group exhibited noticeably elevated levels of Anti-dsDNA, ANA, ESR, CRP, troponin I, APL, and LA ($p<0.001$). While complement component3 (C3) and complement component3 (C4) were significantly lower in Lupus Nephritis group compared to SLE group ($p<0.001$).

Wang et al., (16) had compared LN with non-LN patients, he founded that LN patients had higher blood urea, serum creatinine, and lower Albumin level. There were no significant differences in complete blood count between Non-LN and LN patients. Concordant with the current study Yousef et al., (17) found that quantitative proteinuria was significantly higher in LN group (P value < 0.001) than SLE without nephritis. Also, Samir et al.,(18) showed that patients with nephritis whether active or inactive had significantly low estimated GFR (eGFR) –55.13±12.01 and 61.33±13.67ml/minute in comparison to those patients without nephritis and the control group ($p=0.001$).

The present study found that both ANA titer and Anti-ds DNA titer were statistically significantly higher in LN patients when compared with patients with SLE. This agreed with study of Samir et al. (18) and Emam et al. (19) who found that patients with LN either active or inactive had a statistically significantly higher level of ANA in comparison to those with no LN.

In the current study Platelets count showed significant decline in Lupus Nephritis group compared to SLE group. While TLC was significantly little higher in Lupus Nephritis group compared to SLE group, with no significant difference observed between the two studied groups regarding hemoglobin level.

Abdellatif et al., (20) compared between blood indices of SLE patients regarding to LN patients, found that there was highly statistically substantial enhance in TLC in LN patients compared with those without LN ($P<0.05$). The differential WBCs count revealed highly statistically substantial rise in neutrophils and decrease in lymphocyte counts in LN patients compared to those without LN. The hemoglobin concentration and platelet numbers were not substantially variant in both groups

In the current study, the main immunologic finding was ANA positivity in all cases.

In agreement with Karamehic et al., (21) who found that the incidence of ANA detected by indirect immunofluorescence assay (IFA) method is to be 100% in SLE but unconcordant with Elessawi et al.,(22) who found statistically insignificant but lower prevalence of ANA (18% and 22.9% for LN and SLE without nephritis respectively). Different numbers of the studied population (98 patients) and different genetic background could explain these differences as genetic factors appear to play a role in the risk of different clinical manifestations and antibody production.

We found statistically significant lower C3 and C4 and higher ESR in LN patients.

This is concordant with Elessawi et al., (22) discovered that the primary causes of a lower complement in LN were the increased consumption of C3 and C4 during immune complex formation and the loss of complement in the urine due to proteinuria. Higher ESR reflects the higher inflammatory changes in LN patients and may be explained by the lower serum albumin associated with proteinuria in LN.

As regards CRP, the current study revealed statistically significant higher levels in LN patients. This is concordant with Elshishtawy et al., (23) who found statistically significant higher levels of CRP in LN patients. Higher CRP reflects the higher inflammatory changes in LN patients.

In the current study troponin I showed significant elevation in Lupus Nephritis

group compared to SLE group ($p<0.001$). This is concordant with Divard et al., (24) who found that SLE patients with nephritis had higher percentage of detectable troponin I.

In the current study Antiphospholipid Antibodies (APL) and Lupus Anticoagulant (LA) showed significant elevation in Lupus Nephritis group compared to SLE group ($p<0.001$). This is agreement with Loizou et al., (25) who found higher aCL levels in LN compared with non-renal SLE patients.

In addition, HbA1c was significantly little higher in the SLE group compared to Lupus Nephritis group. SLE patients are associated with insulin resistance and are at higher risk of developing diabetes mellitus (DM). A study by Bruce., (26) had reported the co-existence of DM and SLE.

In terms of MOCA score, the current study demonstrated that the median MOCA score in the Lupus Nephritis group was 23 (20-25), whereas the median MOCA score in the SLE group was 27 (26-28). There was a significant difference in cognitive impairment prevalence between the two groups. Cognitive impairment was observed in 81.4% of Lupus nephritis patients and 14% of SLE patients ($p<0.001$), suggesting a strong association between cognitive impairment and Lupus nephritis.

The prevalence of CI greatly varied between different studies. Sanna et al., (27) and Hanly et al., (15) study reported the lowest percentages (11% and 6%, respectively); however, their results could have been affected by the retrospective study design. Afeltra et al., (28) reported in 2003 a prevalence of 52% of CI, which was significantly associated with higher levels of anti-PL antibodies.

Kim et al., (29) founded that among the different neuropsychiatric manifestations, CI is one of the most common with an estimated prevalence of up to 38 % of SLE patients .CI is also one of the most debilitating manifestations, negatively impacting quality of life and participation in social life.

Also, Raghunath et al.,(30) had revealed that the median MoCA score was 26 (range: 19–30) in SLE cases, that the prevalence of cognitive impairment in the SLE group varied from 19% to 52% .

In the Lupus Nephritis group, the current study found that 30 (42.9%) cases had Lupus Glomerulonephritis class IV. The median Activity index was 23 (20- 25) while the median chronicity index was 1 (0- 3).

In addition, Barathi et al.,(31) revealed in their study that , lupus nephritis staging was done using ISN-RPS classification, which showed classes I (n=3; 7.9%), II (n=9; 23.7%), III (n=9; 23.7%), and IV including the combined class V LN (n=17, 44.7%). The majority were in class IV group (n-14, 36.8%).

In the Lupus Nephritis group, the current study found a significant positive correlation between MOCA score with estimated Glomerular Filtration Rate (eGFR), complement component 3 (C3) and complement component 4 (C4) So, lower eGFR, C3 and C4 contribute to cognitive impairment in lupus nephritis.

A study by Levassort et al., (32) founded that a lower eGFR in chronic kidney disease (CKD)patients was associated with early impairments in certain cognitive domains: praxis, language and attention domains before an obvious cognitive decline.

In Lupus Nephritis group, the current study found a significant negative correlation was found between MOCA score with Systolic Blood Pressure (SBP) ,Diastolic Blood Pressure (DBP), blood urea , serum creatinine, Total Leukocyte Count (TLC), Erythrocyte Sedimentation Rate (ESR) , C-Reactive Protein (CRP), Antiphospholipid Antibodies (APL) , Lupus anticoagulant (LA), Protein /creatinine ratio (PCR), Albumin/creatinine ratio (ACR), 24h urine protein, activity index and chronicity index.

Babroudi et al., (33) investigated the association between blood pressure and cognitive impairment in patients with chronic kidney disease using data from the Chronic Renal Insufficiency Cohort study, which rigorously measured SBP and DBP and administered the modified mini-mental state longitudinally at regular intervals. He founded that - Among CKD, higher baseline SBP was associated with a higher risk of incident cognitive impairment (CI).

The inflammatory response could play a key role in cognitive impairment. A higher TLC count, even within the normal range, was found to be related to the worse psychomotor cognitive performance in the elderly. C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) has been solidly linked as a risk factor for cognitive impairment, A meta-analytic review by Shan et al.,(34) showed that patients with cognitive impairment had CRP levels that were 14 % higher than those of control subjects without cognitive impairment .

Antiphospholipid antibodies-mediated non-inflammatory vascular mechanism resulting in the development of micro-thrombi in the brain, with subsequent ischemia and cell death in the segment involved. This mechanism essentially explains the focal manifestations of NPSLE. Kozora et al., (35) study founded that the presence of aPL in SLE patients has been associated with greater impairment in memory, visuomotor speed, and Visuoconstructional. A relationship between persistently elevated aPL and cognitive impairment has also been reported in SLE. The prevalence of positive aPL in patients with SLE is approximately 30–40%.

Albuminuria is also a risk factor for cognitive impairment. Several prior studies have examined the association of

urine albumin with both cognitive function and structural brain findings. Weiner et al., (36) reported that in a study of 335 homebound elders, albuminuria was associated with poorer executive function (but not memory) and a greater burden of white matter hyperintensities, a marker of early cerebrovascular disease.

A study by Fasano et al., (37) investigates the distribution and determinants of CI in patients with lupus nephritis and compares cognitive function with that in patients with other forms of glomerular chronic kidney disease (CKD) by the Montréal Cognitive Assessment (MoCA). They found that active nephritis and disease duration were associated with poor cognitive performance. GFR values and other parameters evaluated (end stage renal disease, damage, age at diagnosis, use of glucocorticoids, hydroxychloroquine and immunosuppressive drugs) had no significant effect on development of CI in SLE patients.

The current study found that MOCA scores show a significant difference among the different lupus nephritis classes and SLE without nephritis ($p< 0.001$). SLE without nephritis had the highest cognitive function (26.96 ± 1.31), whereas lupus nephritis class IV showed the lowest scores (19.37± 3.43), indicating severe cognitive impairment. Pairwise comparisons revealed that class IV had significantly lower scores than class I ($p= 0.010$), highlighting the impact of severe nephritis on cognitive decline. However, no significant differences were observed between class I and SLE without nephritis ($p= 0.852$) or between class I and class II ($p= 0.241$) or between class I and class III ($p= 0.110$).

Inglese et al., (38) study showing that class I LN is characterized by mesangial immune deposits in Immunofluorescence (IF), but no morphological changes in light microscopy, according to the classification of ISN/RPS 2004. Urinary abnormalities are minimal and include microscopic hematuria with mild proteinuria, while renal function is normal. This is the mildest glomerular lesion in LN and is relatively rare, since these patients generally have no essential clinical renal abnormalities and are not referred to nephrologists for biopsy.

In Catalina et al., (39) study class IV LN includes active or inactive diffuse segmental and/or global endocapillary and/or extra capillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits with or without mesangial alterations. These patients have the most severe and active clinical renal presentation. Proteinuria can reach nephrotic level, and many patients (up to 50%) can present with nephrotic syndrome. Urine sediment is active, while red blood cell (RBC) casts are common.

In Inglese et al., (38) study, patients with lupus nephritis often have more severe

systemic disease, which may increase the risk of neuropsychiatric manifestations, including cognitive impairment. The histopathological classification of lupus nephritis (e.g., Class III, IV, or V) reflects the severity of kidney involvement, which may correlate with overall disease activity and systemic inflammation.

The current study found that Montreal Cognitive Assessment (MOCA) is a valuable tool for detecting cognitive impairment in lupus nephritis with 81.4% sensitivity and 86% specificity. The positive predictive value (PPV) is 89.1% and its negative predictive value. (NPV) is 76.8% (AUC= 0.938 & p <0.001).

Paez et al., (40) compare the efficacy of three screening tests (Montreal Cognitive Assessment [MoCA], Mini Mental State Examination [MMSE], Cognitive Symptom Inventory [CSI]) against the gold standard (neuropsychological battery), to identify the most efficient screening test for cognitive impairment in patients with SLE. Founded that MoCA is a brief, easily applied screening test that is highly effective for detecting cognitive impairment in SLE patients. It could be useful in clinical follow-up as a tool for early detection of cognitive alterations. MoCA presented the strongest correlation with the gold standard (AUC = 99.4%, rs = 0.786, p < 0.001), followed by the MMSE, which showed a moderate correlation (AUC = 92.6%, rs = 0.505, p < 0.001). Of the three screening tests, the CSI showed the least significant correlation with the gold standard (AUC = 30.6%; rs = 0.310, p < 0.05) and the highest sensitivity and specificity were obtained with the MoCA test.

This study's limitations include its lack of neuroimaging studies, and small number of included patients. Likewise, the use of a comprehensive neuropsychological battery could offer a more accurate evaluation. However, such batteries are costly and time consuming and according to several studies, the MoCA may be a suitable screening tool for detecting cognitive impairment in SLE. In addition, no previous studies had investigated MOCA score in lupus nephritis, this study was the first to evaluate this score and its relation to lupus activity.

Conclusion

In comparison to the SLE group, the MOCA score for the LN group was significantly lower. The current study found a significant positive correlation between the MOCA score and eGFR, C3, and C4, and a significant negative correlation with SBP, DBP, urea, creatinine, TLC, ESR, CRP, APL, LA, PCR, ACR, 24h urine protein, activity index, and chronicity index in the Lupus Nephritis group. So, these findings are contributing factors to cognitive impairment in lupus nephritis.

MOCA scores show a significant difference among the different lupus

nephritis classes and SLE without nephritis. SLE without nephritis had the highest cognitive function, whereas lupus nephritis class IV showed the lowest scores indicating severe cognitive impairment.

Montreal Cognitive Assessment (MOCA) is a valuable tool for detecting cognitive impairment in lupus nephritis with 81.4% sensitivity and 86% specificity.

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Conflicts of interest

No conflicts of interest

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