# Assessment of Cognitive Impairment in Systemic Lupus Erythematosus Using the Mini-Mental Status Exam and the Montreal Cognitive Assessment Test-Filipino Version

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## Abstract

**Introduction:** Cognitive impairment (CI) in patients with systemic lupus erythematosus (SLE) presents with or without overt signs of central nervous involvement. The prevalence of CI is variable, ranging from 19-80%. It is often overlooked, leading to high healthcare costs and productivity loss. The usual tools for detection are expensive, time-consuming and not locally available. Detection of CI using the Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment Test (MoCA) is more clinically relevant and practical. The objectives of this study are to determine the prevalence of CI in SLE patients using MMSE/MoCA, to determine the degree of impairment in the different cognitive domains, and to characterize patients with CI in terms of disease activity, education, and employment.

**Methods:** This is a cross-sectional study of 62 SLE patients, 19 years or older, at a rheumatology clinic. Demographic and disease characteristics were collected. The validated Filipino versions of the MMSE/MoCA test were administered. Descriptive and non-parametric statistics were applied.

**Results:** Most patients are female (96.77%), below collegiate level of education (58.06%), and unemployed (70.97%). Mean disease duration is 8.92 (SD±7.03) years. Mean age at diagnosis is 28 (SD±10.30) years. Hypertension is the most common co-morbidity. Most have low lupus disease activity or are in remission (80.65%). Most are on prednisone (72.58%), with an average dose of 11.88mg/day (SD±10.66). The prevalence of CI is 38.71% (MMSE-P) and 77.42% (MoCA-P). The presence of CI is not related to educational level, employment, and disease activity.

**Conclusion:** Cognitive impairment (CI) is common in this cohort of SLE patients. Disease activity, level of education and employment do not seem to affect its occurrence. The MMSE-P and MoCA-P are rapid tools to assess the presence of CI and should be used in clinical practice to improve the quality of care for patients with lupus.

**Keywords:** systemic lupus erythematosus, cognitive impairment, mini mental state examination, montreal cognitive assessment test, neuropsychiatric lupus, cns lupus, philippines

## Introduction

Systemic lupus erythematosus (SLE) is a chronic, relapsing-remitting autoimmune disease which involves several organs and has variable clinical signs and symptoms with severity ranging from mild and transient to fatal. Cognitive impairment (CI) is seen in SLE, and this involves patients with or without documented or overt signs of central nervous system (CNS) involvement. It is postulated that the cognitive disorder is the result of underlying brain disease. However, the exact mechanisms are yet to be understood. The prevalence and degree of CI is highly variable among different cohorts.

In the San Antonio Lupus Study Neuropsychiatric Disease (NPSLE) with 128 unselected subjects, 80% were found with one or more of the NPSLE syndromes. In a subset of 67 patients using standardized neuropsychiatric testing, 21% had normal results and six percent had severe impairment. They concluded that NPSLE was common; headache, cognitive dysfunction and psychiatric disorders were the dominant syndromes.[1] Another study using ACR case definitions on 61 SLE patients found a NPSLE prevalence of 72%. The most common neuropsychiatric problem was cognitive dysfunction (52%), followed by mood disorders (27%), cerebrovascular disease (24%), and headache (21%). When patients with mild deficits (less than three impaired domains) were not considered, the prevalence of cognitive dysfunction decreased from 52% to 21%.

Factors which affect CI in SLE patients have been described. Prevalence of NPSLE was higher in patients with APAS.[2] High disease activity was predictive of psychosis and CI.[3] Daily stress experienced for the past six months has the greatest explanatory predictive power on the scores for delayed recall visual memory, visual fluency and attention speed and this was an effect which was not found in emotional variables such as depression and anxiety.[4] In a large study

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evaluating the predictors of cognitive dysfunction in patients with SLE, declining cognitive dysfunction was associated with consistently positive anti-phospholipid antibodies, consistent prednisone use, diabetes, higher depression scores, and less education.[5] Socio-demographic data (Table I) are also important variables.[6]

There are two validated tools for detecting cognitive dysfunction in SLE patients. The first is traditional neuropsychologic testing (NPT), which consists of a variable battery of tests, administered and interpreted by a clinical psychologist requiring four to six hours to complete, and costs $1000 in the United States.[7,8] The second is the Automated Neuropsychologic Assessment Metrics (ANAM), a computerized battery of tests, requires approximately 45 minutes, and costs approximately $400 for a software license.[9,10] The ANAM has been used in several studies in SLE.[11,12,13,14] While more efficient and less costly, the ANAM is neither readily available nor practical for clinic administration or for screening larger populations.

The Mini Mental State Examination (MMSE)[15] is the most commonly used instrument for screening cognitive function. It also tracks changes in cognitive functioning over time and may be used to assess the effects of therapeutic agents.[16] Several publications demonstrate it to be a relatively sensitive marker of overt dementia.[17,18,19] However, the utility decreases in patients with mild cognitive decline and psychiatric conditions.[20,21,22] Analysis of both MMSE subtest and total scores may increase the sensitivity of the MMSE for screening mild CI and its subtypes.[23]

The Montreal Cognitive assessment (MoCA) test is also a popular cognitive screening test designed to detect mild CI in adults.[24] It can be administered in approximately 10 minutes. It is a performance-based questionnaire with fair sensitivity (85-90%) and variable specificity (53-87%) in a number of diseases. It was originally validated in a normative sample with a mean education of 13.3. A score of 26 or above is considered normal. A follow-up study to obtain normative data in a sample with 12 years or less of education recommended the addition of one point for 10-12 years of education and two points for four to nine years of education. The MoCA was adapted and translated in Filipino, taking into account the effect of culture and language in its adaptation.[25] When used for cognitive assessment of elderly Filipino patients, it was found to be reliable, with a high level of internal consistency, and a positive but low correlation with the MMSE.[26]

In detection of mild CI (n=94 subjects), the MoCA test has sensitivity and specificity of 90% and 87% respectively while MMSE has 18% and 100%.[22] When used in lupus patients, it had significant correlation with the gold standard ANAM and has a sensitivity of 83% and a specificity of 73%.[27]

There is mild CI in one-fifth of lupus patients and this may easily be missed if screening is not done.[28] Undetected CI materially contributes to work disability.[29] In a study on Chinese patients with SLE, memory loss (51%) was one of the most common self-reported reasons for loss of job.[30] It also has negative impact on adherence with treatment, disease control, health care costs, and quality of life.[31]

Although cognitive function of patients with SLE has been studied well in other populations, their results cannot be extrapolated to the Filipino patient because of the important effect of culture on neuropsychological tests.[32] Furthermore, there is considerable variability on affected cognitive domains.[33] This underlines the need to study our own patients, determine the prevalence of CI, understand their disease better, and enable us to improve care.

We hypothesized that CI is prevalent in our own cohort of lupus patients. The MMSE and MOCA have been used extensively to detect CI in lupus and several other clinical conditions and we expect them to detect CI based on previous published rates.

The general objective is to determine the prevalence of CI in a cohort of SLE patients at the rheumatology clinic of a tertiary government training hospital in the Philippines. More specifically, this paper presents the demographics, disease characteristics, and treatment of the study population. Furthermore, it aims to determine the prevalence and type of CI (based on subtype domains) using the MMSE and the Montreal Cognitive Assessment Test Philippine Version (MoCA-P). Finally, it determines the association of CI with lupus disease activity (using the MEX-SLEDAI), education and employment.

## Methods

This was a cross- sectional study of patients 19 years old and above, diagnosed with SLE based on the American College of Rheumatology 1997 criteria[34] being followed up in the rheumatology clinic of a tertiary government hospital. After obtaining informed consent, the patients were interviewed and examined. The Mini-Mental State Examination Philippine Version (MMSE-P) and the MoCA-P were both administered. The following data were recorded in a data collection form: demographics (age, gender, civil status, BMI, educational attainment, employment status, smoking and alcohol history), disease characteristics (age of onset of disease, duration of disease, presence of comorbidities, MEX-SLEDAI disease activity score), and medications at the time of consult.

This is an 11-part examination which tests orientation to time and place, registration, attention, recall, language naming, repetition, three-stage verbal command,

**Table I. Demographic characteristics of the sample population**

| | Results n= 62 |
|---|---|
| Mean age at consult (SD) | 37.06 (11.38) |
| Mean BMI (SD) | 24.01 (5.11) |
| Female sex | 60 (96.77%) |
| Civil status | |
| Single | 27 (43.55%) |
| Married | 28 (45.16%) |
| Separated | 3 (4.84%) |
| Widow/er | 3 (4.84%) |
| Common law | 1 (1.61%) |
| Education | |
| Elementary | 4 (6.45%) |
| High school | 17 (27.42%) |
| College | 26 (41.94%) |
| Vocational | 15 (24.19%) |

comprehension of written command, writing and copying. The maximum score is 30 and a score of less than 27 correlates with CI. The MMSE was translated in Filipino in a validation study in 2003.[35]

The MoCA test is a one page, 30-point test administered in approximately 10 minutes (www.mocatest.org). It has been translated into the Filipino language and validated. There are eight items testing different aspects of cognition, namely, visuospatial (Alternate Trail Making), visuoconstructional (Cube and Clock), naming, memory, attention (forward digit span, backward digit span, vigilance, serial 7s), language (Sentence Repetition and Verbal Fluency), abstraction, delayed recall and orientation.

Descriptive statistics including means, standard deviations and percentages were obtained. Association of factors with CI was analyzed using non-parametric statistics (Chi-Square Test, Fisher's Exact Test). A *p*-value of less that 0.05 was considered significant for all the analyses.

The conduct of this study was approved by the University of the Philippines Manila Research Ethics Board (UPMREB) Philippine General Hospital Panel. As the authors are also the primary care givers of the patients involved in the study, the patients were informed of their scores after testing, including the interpretation of those scores. The results of the study shall be used to guide individual patients' management, and shall guide referral systems and further testing of those with CI as warranted.

## Results

A total of 62 SLE patients were included in this study. This sample size was required assuming a 95% level of confidence that the proportion of impairment is within 80±10%. The mean age at the time of test administration (consult) is 37.06 yrs. The median age is 36. The majority of the patients were females (96.77%), married (45.16%), and had college education (41.94%).(Table I) Disease characteristics are summarized in Table II. The average disease duration is 8.92 years. The average age at diagnosis of SLE was 28 years old, the diagnosis made approximately 0.53 year from the onset of symptoms. At the time of diagnosis, most patients

**Table II. Disease Characteristics**

| | |
|---|---|
| Disease duration, in years (SD) | 8.92 (7.03) |
| Mean age at diagnosis of SLE, in years (SD) | 28.15 (10.30) |
| Mean time to diagnosis, in years (SD) | 0.53 (1.09) |
| ACR criteria fulfilled at diagnosis | |
| Arthritis | 55 |
| ANA | 54 |
| Malar rash | 49 |
| Photosensitivity | 41 |
| Discoid rash | 39 |
| Oral ulcers | 35 |
| Hematologic | 25 |
| Renal | 22 |
| Immunologic | 10 |
| Serositis | 8 |
| Neuropsychiatric | 4 |
| MEX-SLEDAI disease activity score on consult | |
| <6 | 50 (80.65%) |
| ≥6 | 12 (19.35%) |
| Disease activity involvement on consult | |
| Mucocutaneous | 12 |
| Renal | 11 |
| Arthritis | 4 |
| Leukopenia/Lymphopenia | 4 |
| Neurologic | 3 |
| Fever/Fatigue | 2 |
| Vasculitis | 2 |
| Hemolysis | 1 |
| Comorbid conditions | |
| Hypertension | 20 |
| Diabetes mellitus | 7 |
| Anti-phospholipid antibody syndrome | 7 |
| Kidney disease | 6 |
| Dyslipidemia | 6 |
| Tuberculosis | 5 |
| Bronchial asthma | 5 |
| Stroke | 4 |
| Abnormal uterine bleeding | 2 |
| Allergic rhinitis | 1 |
| Thyroid disease | 1 |
| Seizure disorder | 1 |
| Immunosuppressive medications | |
| Prednisone | 45 |
| Mean prednisone dose in mg (SD) | 11.88 (10.66) |
| Hydroxychloroquine | 29 |
| Cyclophosphamide | 3 |
| Mycophenolate mofetil | 6 |
| Azathioprine | 3 |
| Methotrexate | 1 |
| Biologics | 1 |
| Other medications | |
| Anti-hypertensive | 24 |
| Anti-diabetes | 6 |
| Lipid lowering treatment | 6 |
| Aspirin | 5 |
| Warfarin | 2 |

**Table III. Prevalence and mean scores for Mini Mental State Examination-P (n=62)**

| | Definition/Instruction/Scoring | Perfect Score | Mean Score (SD) |
|---|---|---|---|
| Overall | Total score | 30 | 26.90 (2.68) |
| Orientation to time | 1 point per correct answer;<br>From the broadest to most narrow<br>(Season - Date - Year – Month – Day) | 5 | 4.76 (0.47) |
| Orientation to place | 1 point per correct answer;<br>From the broadest to most narrow<br>(Country – Town/City – Street – Floor – Building) | 5 | 4.73 (0.55) |
| Registration | 1 point per correctly repeated word<br>Repeating named prompts<br>(Mango – Table – Money; "Mangga – Mesa – Pera") | 3 | 2.94 (0.31) |
| Attention | 1 point deducted for each letter misspelled<br>The word "KARNE or CARNE" to be spelled then spelled backwards | 5 | 4.34 (1.57) |
| Recall | 1 point per correct answer<br>Registration recall of the 3 words<br>(Mango – Table – Money; "Mangga – Mesa – Pera") | 3 | 1.84 (1.18) |
| Language naming | 1 point per correct answer<br>Naming a pencil and a watch | 2 | 2.00 (0) |
| Repetition | 1 point for correctly repeated phrase<br>Speaking back a phrase ("Minikaniko ni Monika ang Makina") | 1 | 0.63 (0.49) |
| 3-Stage verbal command | 1 point per correctly followed command<br>1. Get the paper with your right/left hand ("Kunin ang papel gamit ang kanan/kaliwang kamay")<br>2. Fold it in the middle/into half ("Tiklupin sa gitna o kalahti")<br>3. Place the paper on your lap ("Ilagay ang papel sa kandungan") | 3 | 2.94 (0.25) |
| Comprehension | 1 point for correct answer<br>Read and do the instruction ("Basahin at gawin")<br>Close your eyes. ("Ipikit mo ang iyong mga mata") | 1 | 0.97 (0.18) |
| Writing | 1 point for correct answer<br>Write a sentence. ("Magsulat ka ng isang pangungusap") | 1 | 0.97 (0.18) |
| Copying | 1 point for correct answer<br>Copy this. (Kopyahin ito) – interlocking polygon | 1 | 0.81 (0.40) |

**Table IV. Mean scores for Montreal Cognitive Assessment Examination-P (n=62)**

| | Definition/Instruction | Perfect Score | Mean Score (SD) |
|---|---|---|---|
| Overall | Total score without factoring educational attainment | 30 | 21.16 (4.47) |
| Overall, adjusted for education | Total score while factoring educational attainment<br>1 point is added is ≤12 yrs of education | 30 | 22.00 (4.27) |
| Visuospatial/executive | Trail-making (alternation) task<br>Three dimensional cube copy<br>Clock drawing (10 minutes past 11) | 5 | 3.21 (1.51) |
| Naming | Three item naming confrontation task with low familiarity animals (lion, owl, camel) | 3 | 2.52 (0.82) |
| Attention<br>Forward<br>Backward<br>Vigilance<br>Serial 7s | Sustained attention task which consists of:<br>5 digits read forward<br>3 digits read backward<br>Target detection (of letter A) using tapping<br>Serial subtraction task | <br>1<br>1<br>1<br>3 | 5.89 (1.98)<br>0.90 (0.30)<br>0.69 (0.46)<br>0.66 (0.48)<br>2.35 (0.89) |
| Language<br>Sentence<br>Repetition<br>Verbal fluency | <br>Repetition of 2 syntactically complex sentences<br><br>Phonemic fluency demonstrated as ability to enumerate ≥ 11 Filipino words starting with the letter "B" over 1 minute | <br>2<br>1 | <br>0.65 (0.66)<br>0.63 (0.49) |
| Abstraction | Two-item verbal abstraction task (Similarity of train and bicycle, weighing scale and ruler) | 2 | 1.71 (0.58) |
| Delayed recall | Second part of the memory recall task. The first part consists of a learning trial of 5 nouns ("Mukha, Asul Simbahan, Rosas, Seda"). This is to be repeated after approximately 5 minutes. Items recalled without cues are given 1 point each. | 5 | 2.00 (1.59) |
| Orientation | Orientation to time (date, month, year, day) and place (location/building, city) | 6 | 5.84 (0.52) |

**Table V. Comparison table (MMSE)**

| MMSE | With Cognitive Dysfunction | Without Cognitive Dysfunction | *p*-value |
|---|---|---|---|
| High mex SLEDAI | 3 | 9 | Chi 0.28 Fisher 0.33 |
| Low mex SLEDAI | 21 | 29 | |
| | | | |
| Low education | 20 | 25 | Chi 0.13 Fisher 0.16 |
| High education | 4 | 13 | |
| | | | |
| Unemployed | 18 | 26 | Chi 0.58 Fisher 0.77 |
| Employed | 6 | 12 | |

**Table VI. Comparison table (Moca-P)**

| MOCA | With Cognitive Dysfunction | Without Cognitive Dysfunction | *p*-value |
|---|---|---|---|
| High mex SLEDAI | 10 | 2 | Chi 0.50 Fisher 0.71 |
| Low mex SLEDAI | 37 | 13 | |
| | | | |
| Low education | 34 | 11 | Chi 0.94 Fisher 1.00 |
| High education | 13 | 4 | |
| | | | |
| Unemployed | 32 | 12 | Chi 0.38 Fisher 0.52 |
| Employed | 15 | 3 | |

**Table VII. MMSE and MoCA-P scores of patients with NPSLE at onset**

| Neuropsychiatric presentation | MMSE | MoCA-P |
|---|---|---|
| Behavioral change | 30 | 22 |
| Stroke in the young | 28 | 22 |
| Seizures | 30 | 15 |
| Transverse myelitis | 24 | 8 |

**Table VIII. MMSE and MoCA-P scores of patients with neurologic activity on test administration**

| Neurologic activity | MMSE | MoCA-P |
|---|---|---|
| Lupus headache | 30 | 22 |
| Lupus headache | 28 | 22 |
| Transverse myelitis | 30 | 15 |

presented with arthritis, photosensitivity, malar and discoid rash and a positive anti-nuclear antibody test. The most common comorbid conditions were hypertension, diabetes mellitus, and anti-phospholipid antibody syndrome. The most frequent immunosuppressive medication was prednisone (72.58%), with an average dose of 11.88 mg/day. Less than half of the patients were on hydroxychloroquine. A large percentage of the subjects had low disease activity or were in remission (80.65%) when the study was conducted. Among those with high disease activity, renal and mucocutaneous manifestations were the most common. Three patients had neurologic manifestations (transverse myelitis and lupus headache).

There were 24 patients (38.71%) who had CI based on the MMSE (Table III). Most of the patients scored well on orientation to time (4.76) and place (4.73), registration (2.94) and language naming (2.00). However, they scored poorly on repetition (0.63). Using the MoCA-P (Table IV), 48 patients (77.42%) had CI after adjustment for level of education. Most patients struggled in visuospatial/executive (3.21), attention (5.89), and delayed recall (5.84). Using univariate analysis, we found that disease activity, level of education and employment status did not significantly affect cognitive function as measured using either the MMSE-P or the MoCA-P (Table V and VI).

## Discussion

As hypothesized, this study shows that CI is common in this cohort of SLE patients. The cognitive domains in which the patient had poor scores were repetition in MMSE-P and visuospatial/executive function, attention and delayed recall in MoCA-P. This is similar to the study by Skeel (2010) where impairment involved expressive language, attention and speed of processing.[34] However, in contrast to Skeel's population, our cohort of patients had impaired memory (poor scores in repetition and delayed recall). This finding is similar to a study by Cavaco (2012), which showed that verbal memory, psychomotor speed and olfaction are vulnerable to dysfunction in NPSLE.[36]

Disease activity, level of education and employment were related to CI. The absence of correlation is similar to a previous study which reported that disease activity and prednisone dose does not correlate with CI in SLE.[37] However, the lack of correlation between level of education and cognitive function was unexpected.[31] It is possible that the difference may lie in the fact that this cohort had a relatively homogenous educational status or the sample size may be insufficient to show a difference. The absence of significant correlation between disease activity and CI may suggest that the dysfunction may represent the consequences of a chronic disease rather than acute CNS damage brought about by inflammation.[38]

We examined the subset of patients who initially presented with neuropsychiatric manifestations during the time of lupus diagnosis (n=4). The presentations were seizures, behavioral change, cerebrovascular infarct and transverse myelitis (Table VII). Only the patient who presented with transverse myelitis had a low MMSE score. However, the MoCA-P scores of all these patients showed CI. We also looked at the subset of patients (n=3) who had active neuropsychiatric disease manifestations (lupus headache and transverse myelitis (Table VIII). The two patients who has lupus headache had MMSE scores of 28 and 29 (both corresponding to normal cognitive function), while the one patient with transverse myelitis had an MMSE score of 24,

signifying CI. This differs with their MoCA-P, scores where both patients with lupus headache had scores 23 and the patient with transverse myelitis has a score of eight, all signifying CI. The difference in detection is likely due to the MoCA-P being more superior in detecting even mild CI.[24]

The results of this study should open up interest in further research on the topic. Future directions of the study can take a look at other variables such as length of use and dose of prednisone, presence of APAS and coexisting anxiety, depression or mood dysfunction. While the dose of prednisone and presence of coexisting APAS were recorded, they were not included in the analysis because not all patients included in the study were on prednisone and some of those who had a diagnosis of APAS did not have serologic confirmation. These, as well as the small sample size, were the limitations of the paper which can be improved upon in future studies. The MMSE and MoCA-P were designed to be clinical tools for both diagnosing and following up patients and using them to measure CI over time may also be a topic for further research.

## Conclusion

The prevalence of CI in our cohort of lupus patients is high. This means that patients can do relatively well, without overt neurologic symptoms or severe disease activity and still have significant CI. This is important to determine as cognitive decline can lead to poorer self-care or compliance to treatment. MMSE-P and MoCA-P are rapid tools that can effectively assess the presence of CI. As the results of the subgroup analysis have shown, MoCA-P may be better in detecting mild CI and may be the better tool in catching patients who would have a normal MMSE. These tools are easy to use and are recommended be part of the standard of care of lupus patients in clinical practice. Adherence to treatment, ability to return to or sustain employment, productivity, and over-all quality of life of patients with lupus may be improved if CI is detected and addressed. Further studies involving a larger population are needed to definitely establish the effect of factors on this CI.

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