ORIGINAL RESEARCH

Psychiatric Manifestations of Systemic Lupus Erythematosus Patients in a Tertiary Care Hospital: A Cross-sectional Study

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Abstract

Aim and background: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with diverse neuropsychiatric manifestations which are classified and diagnosed under ACR 1999 guidelines and contribute significantly to overall disease morbidity and mortality. Data are scarce regarding neuropsychiatric manifestations of SLE in Eastern India as well as the utility of psychiatric rating scales for classifying, assessing disease severity, and prognostication. This study focuses on deriving the prevalence of psychiatric manifestations among SLE patients and their correlation with disease severity using several psychiatric rating scales and markers of disease severity.

Methods: This is a single center-based cross-sectional study involving 50 consented adult SLE patients fulfilling Systemic Lupus Erythematosus International Collaboration Committee (SLICC) criteria at NRS Medical College & Hospital over 18 months using a pretested questionnaire that includes psychiatric rating scales as well as disease severity assessment tools. Patients with drug abuse, pre-existing psychiatric disorders, dyselectrolytemia, and ongoing infection were excluded from the study.

Results: All the participants had anxiety disorder (100%) followed by depression (80%), psychosis (58%), mood disorders (54%), and cognitive dysfunction (8%). Systemic lupus activity measure, revised (SLAM-R) score had a positive correlation with General Health Questionnaire (GHQ) ($r = 0.518$, $p < 0.05$) and brief psychiatric rating scale (BPRS) ($r = 0.589$, $p < 0.05$). Brief psychiatric rating scale and GHQ had a positive correlation between them ($r = 0.774$, $p < 0.05$).

Conclusion: Psychiatric manifestations of SLE are quite prevalent in the study niche and their clinical severity is comparable to that estimated using screening questionnaires and disease severity tools used in this study.

Clinical significance: This study showed positive implications of implementing psychiatric rating scales as a screening tool in SLE patients for early diagnosis of psychiatric manifestations and use as corroborative measures of disease severity.

Keywords: Brief psychiatric rating scale, General health questionnaire, Hamilton anxiety rating scale, Hamilton depression rating scale, Neuropsychiatric systemic lupus erythematosus, Psychiatric manifestations, Psychosis, Systemic lupus activity measure, revised, Systemic lupus erythematosus, Systemic lupus erythematosus international collaboration committee.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with diverse clinical manifestations including some life-threatening organ dysfunctions. Neuropsychiatric systemic lupus erythematosus (NPSLE) encompasses a wide range of focal and diffuse central and peripheral nervous system disorders along with an array of psychiatric manifestations. Psychiatric manifestations as charted in American College of Rheumatology (ACR), 1999 Ad hoc committee[1] classification system included five entities viz. anxiety disorder, cognitive dysfunction, mood disorders, psychosis, and acute confusional state. Though poorly understood, two underlying pathologic processes have been proposed for NPSLE, namely (a) autoimmune/inflammatory pathway leading to the intrathecal immune complex formation or disruptions of blood–brain-barrier (B-B-B), and (b) ischemic or thrombotic pathway leading to cerebral microangiopathy, accelerated atherosclerosis, vascular occlusion, and hemorrhage. Psychiatric manifestations are conglomerated manifestations of diffuse brain injuries as well as active disease processes and the severity of each psychiatric manifestation might vary with ongoing disease severity, organ damage, and other socio-environmental factors which are quite difficult to accurately predict with currently available datasets.[2,3]

Anxiety disorders encompass anticipation of danger or misfortune accompanied by apprehension, dysphoria, or tension. This includes generalized anxiety, panic disorder, panic attacks, and obsessive-compulsive disorders. Hamilton anxiety rating scale (HAM-A)[4] can be used to classify and identify anxiety disorders. Their correlation with disease activity is controversial as well as potential reversibility of individual symptoms is not well

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documented.[5,6] Understanding factors other than the active disease process for anxiety disorders is necessary.

Cognitive dysfunction is one of the most common manifestations among NPSLE patients. It implicates significant deficits in any or all the following cognitive domains: simple or complex attention, reasoning, executive skills (e.g., planning, organizing, sequencing), memory (e.g., episodic/declarative, procedural, semantic, learning), visuospatial processing, language (e.g., verbal fluency, naming, comprehension), and psychomotor speed. Mini-mental state examination (MMSE)[7] is a surrogate questionnaire that recognizes cognitive dysfunction and its severity. There is no clear data regarding the correlation between cognitive dysfunction and active disease process as it is not always necessarily due to the primary disease process and not due to secondary thrombotic or vascular events.

Prominent and persistent disturbance in the mood either depressed mood (markedly diminished interest or pleasure in almost all activities) or elevated, expansive, or irritable mood is quite common among NPSLE patients. Depression may be an early symptom of NPSLE and is associated with increased morbidity.[8] To establish a causal relationship with SLE, some common underlying confounding factors like any abnormality in liver or thyroid function, and serum electrolytes need to be ruled out beforehand. It is still controversial whether a causal relationship between the severity of depressive episodes with disease activity in NPSLE patients exists or not.[9,10] Implementing the Hamilton depression rating scale (HDRS) for depression and mood disorder questionnaire (MDQ) for mood disorder can identify these patients and the severity of symptoms which can be further plotted against disease severity assessment tools like systemic lupus activity measure, revised (SLAM-R) to assess their correlation in SLE patients.

Psychosis, in SLE, may present early in the course and resolve within 2–4 weeks but requires early aggressive treatment and is followed by long-term remission in most cases.[11] Corticosteroid-induced psychiatric disorders, delirium, and functional psychosis are some secondary confounders mimicking lupus psychosis. Acute confusional state or delirium is not a rare manifestation of NPSLE and it overlaps with a spectrum of "organic brain syndrome."[12] In our study we have expelled this entity as it cannot be considered a purely psychiatric manifestation. Brief psychiatric rating scale (BPRS) is an effective tool to assess patients with psychosis and their symptom severity.

There is wide variation in prevalence data for psychiatric manifestations worldwide likely due to their overlapping nature, inadequate case definition, or inconsistent use of diagnostic classification systems as well as geographical variation. None of the studies done previously provides a satisfactory prevalence dataset for different psychiatric manifestations of SLE in the eastern Indian population. There is limited data regarding the utilization of various psychiatric rating scales used in our study that have been readily available for years and can be easily implemented for the assessment of the severity of psychiatric manifestations as well as whether they corroborate with active disease processes. This cross-sectional study focuses on bridging that gap by evaluating the prevalence of psychiatric manifestations in SLE, their severity, and their correlation with disease activity by implementing multiple psychiatric assessment tools and disease severity assessment tools (addressed below) in the study questionnaire. We had tried to explore the correlation between psychiatric assessment tools and disease severity assessment tools (SLAM-R) also in this study.

Materials and Methods

This study is a cross-sectional, hospital-based, single-center study conducted between 1 February 2021 to 30 September 2022 (i.e. 18 months) at NRS Medical College & Hospital, Kolkata, with a sample size of 50 patients which was calculated using "census" method. The study was conducted after obtaining informed consent from every participant and was done by the "Declaration of Helsinki."

We included all adult patients (age > 18 years), classified as SLE using the Systemic Lupus Erythematosus International Collaboration Committee (SLICC)[13] classification criteria, visited or admitted at NRS Medical College and given their consent. We excluded patients with a history of any drug abuse, with preexisting psychiatric disorders (including steroid-induced psychosis), having any dyselectrolytemia or any active infection during presentation, from the study. A thorough history and clinical examination of study subjects were performed on a diagnostic one-to-one interview basis before they entered a pretested questionnaire. We used ACR 1999 nomenclature and case definitions of NPSLE for diagnosis of psychiatric manifestations, further confirmed by International Classification of Diseases 10 (ICD10).[14] Basic laboratory evaluations[a] and previous investigations reviewed. The study questionnaire included psychiatric rating scales[b] [HAM-A,MMSE, General Health Questionnaire (GHQ), HDRS, BPRS, MDQ and disease severity assessment tools[c] [SLAM-R, SDI].[4,7,15–19]

Data had been summarized as mean and standard deviation for numerical variables and count and percentages for

[a]Basic laboratory evaluation includes complete blood count, liver function tests, renal function tests, serum electrolytes (sodium, potassium, calcium, magnesium, chloride), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)

[b]Psychiatric rating scales: HAM-A[4]—consists of a set of 14 questions and their answers to be rated on an ordinal scale of *mild* (score 1) to *very severe* (score 4). A score of 17 or less indicates mild anxiety severity. A score from 18 to 24 indicates mild to moderate anxiety severity. Lastly, a score of 25–30 indicates moderate to severe anxiety severity. MMSE[7]—a score less than 23 is considered mild cognitive impairment and a score less than 18 is having severe cognitive impairment. GHQ or General Health Questionnaire[15]—a basic screening tool to ascertain any possibility of having any psychiatric "distress." A score ≥5 using the binary method (where *not at all*, *and No more than usual* score 0, and *rather more than usual and Much more than usual* score 1), has been reported to indicate probable cases of psychiatric distress or *caseness*. Hamilton Depression Rating Scale (HDRS)[16] where a score ≥20 (moderate severity) is considered for entry into clinical trials. BPRS[17] has been used to classify whether psychosis is present or not. A score of 31–40 considered *mild illness*, 41–52 as *moderately ill*, and ≥53 as *markedly ill*. MDQ[18]—a simplified single-page inventory consisting of 13 binary (yes/no) questions for a lifetime history of a manic or hypomanic syndrome and answer "yes" to ≥7 warrants further medical assessment for bipolar disorder.

[c]Disease severity assessment tools: SLAM-R is used which encompasses "constitutional" and "multisystemic" inputs with ratings from "0" to "3" each, resulting in a possible range of 0–81 with a score of 7 being considered clinically significant and effects decision to treat.

categorical variables. For correlation between two numerical variables, we used Pearson's or Spearman's correlation (σ). Results were considered significant if p-value < 0.05 (with 95% confidence interval). Data were represented using pie charts, bar diagrams, and linear distribution graphs wherever applicable. Collected data were analyzed using Statistical Package for Social Science (SPSS) version 22 (SPSS Inc., Chicago, IL, USA).

Results and Analysis

In our studied population, the mean age was 28.1 ± 7.6 years, of which the majority (86%) were females and were predominantly from rural areas (66%). As for their socioeconomic strata, 86% were categorized as middle class, and 14% in poor as per the modified Kuppuswamy socioeconomic scale 2020.[20]

In this study, we included 50 SLE patients, among which the most prevalent psychiatric manifestation was "anxiety disorder" affecting all the patients (i.e. 100%) followed by "depression" ($n = 40$, 80%). These manifestations when further stratified as per severity using respective psychiatric rating scales and the categorical data has been represented in Figure 1.

Patients who had been diagnosed with "anxiety disorders" were on long-standing medication for SLE, and they often complained of frequent verbal altercations with their family members and during social communication. They also complained of "sleepless nights," "tension," generalized body ache that was non-responsive to analgesics, "burning sensation in skull," "dry mouth," "frequent urgency for micturition," and many other "somatic" and "autonomic" symptoms. A patient who was pregnant during our study complained of "hot flushes" during anxiety episodes. Financial burden during treatment along with frequent hospitalization was complained by several patients which made them "worried" and sometimes faced familial catapult.

We had identified 4 (8%) patients with cognitive dysfunction who were on medication for SLE (but not on steroids) and two of them were admitted to the medicine ward. Neuroimaging in the form of a CT scan followed by an MRI was performed which revealed no significant abnormality. Each of them has a good Glasgow coma scale (GCS) of 14 and 15 and no focal neurodeficit. Both had accompanying lupus nephritis and polyarthritis. One of the patients with severe cognitive impairment had associated diffuse systemic sclerosis. Metabolic profiles were within limits during admission.

Patients who were diagnosed with psychosis ($n = 29$, 58%) in SLE had been shown in the majority a combination of paranoid and grandiose symptoms as well as auditory and visual hallucinations. As per BPRS, we had identified 17 patients as "mildly ill (34%)," six patients (12%) each were marked as "moderately ill," and "markedly ill". All the affected patients diagnosed with "psychosis" were psychologically "distressed" (GHQ-28 score ≥ 5). Among psychosis patients, predominant symptoms were grandiosity, somatic symptoms, tension, and unusual thoughts which were present in almost all the patients. Predominant other systemic involvement in patients with lupus psychosis, in our study, was lupus nephritis followed by dermatological involvement and polyarthritis. A statistically significant "damage" (SDI > 0) was present in all psychosis patients.

In our study, mood disorders were present in 27 patients (54%) and statistically significant "psychological distress" was present in all of them. Manic and depressive episodes were frequent in these patients. They were on treatment for the disease process and regular psychiatric follow-up. Mild depression was present in 25 (50%), moderate depression in 7 (14%), and severe depression in 8 (16%) patients in our study population. 14% had no depressive symptoms. Patients with severe depression reported to have suicidal ideation at times.

As per GHQ, we identified that 98% of the study population had "presence of distress" or "caseness" and 2% did not have any. Among the entire study population using the SLE damage index (SDI), we found 84% ($n = 42$) cases had significant damage and when we compared it with the GHQ score, we found mean GHQ score for the presence of "damage" is 26.24 ± 14.48 with $p = 0.004$ which is statistically significant. In our study, the mean BPRS score for patients with "damage" present was 37.05 ± 14.11 which is statistically significant ($p = 0.005$). The mean SDI score for "mild cognitive dysfunction" was 2 ± 0.0 and for "severe cognitive dysfunction" was 5.5 ± 3.54 which is statistically significant ($p < 0.001$) whereas the mean SLAM-R score for mild cognitive dysfunction was 15.00, for severe cognitive dysfunction was 37.5 ± 6.36 ($p < 0.001$). Mean SLAM-R scores for anxiety and depression have been displayed in Tables 1 and 2, respectively.

In our study, 58% ($n = 17$) had "mildly ill" psychosis, 21% ($n = 6$) had "moderately ill" psychosis and 21% ($n = 6$) had "markedly ill" psychosis among SLE patients with psychological distress (GHQ ≥ 5). In this study, the mean BPRS score for patients with "damage" present was 37.05 ± 14.11 which is statistically significant ($p = 0.005$).

We correlated GHQ and BPRS with SLAM-R scores and found that the SLAM-R score had a positive correlation with GHQ ($r = 0.518$, $p < 0.05$) and BPRS ($r = 0.589$, $p < 0.05$). BPRS and GHQ have a positive correlation between them ($r = 0.774$, $p < 0.05$).

Discussion

Psychiatric abnormalities are common in SLE with a prevalence of 17–75%.[8] There is a variable distribution of data regarding the prevalence of psychiatric manifestations in NPSLE patients across different studies done previously[8,21–24] which summarize overall prevalence of anxiety disorders is 4–27%, cognitive dysfunction is 3.9–80% whereas the prevalence of psychosis is 1.9–6.5%, mood disorders is 3.9–48% and major depressive symptoms are 4–21%. It was found that all the patients ($n = 50$, 100%) in our study population who were diagnosed with SLE had at least one psychiatric manifestation. This exceptionally high prevalence may partially be imparted upon the diagnostic and classification criteria for psychiatric manifestations in NPSLE includes a large array of manifestations that overlap very often and are very difficult to distinguish.

We have found that the majority of the population had "psychological distress" (GHQ score ≥5, $n = 49$, 98%) and anxiety disorders and depression are major manifestations. Among patients with "anxiety disorders," the majority had mild anxiety ($n = 31$, 62%) and these patients were more anxious may be due to increasing awareness of the disease, the course of ongoing

SLE damage index (SDI) is a scale to measure organ damage occurring since diagnosis of SLE, ascertained by clinical assessment, and should at least be present for the last six months. At diagnosis (by definition), the SDI score is 0. Damage due to disease is considered if the score is ≥1.[19]

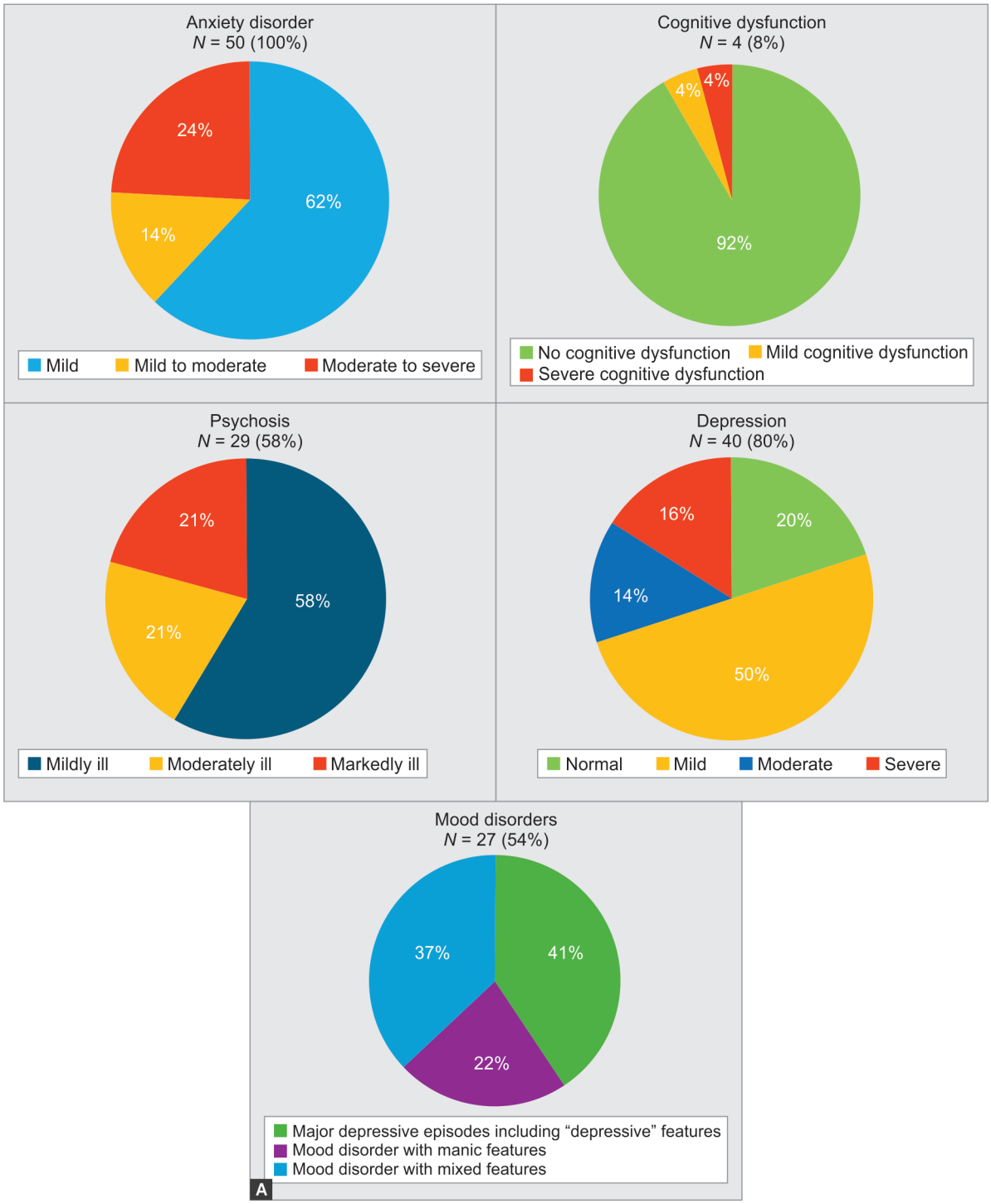

Fig. 1A: Prevalence data for individual psychiatric manifestations

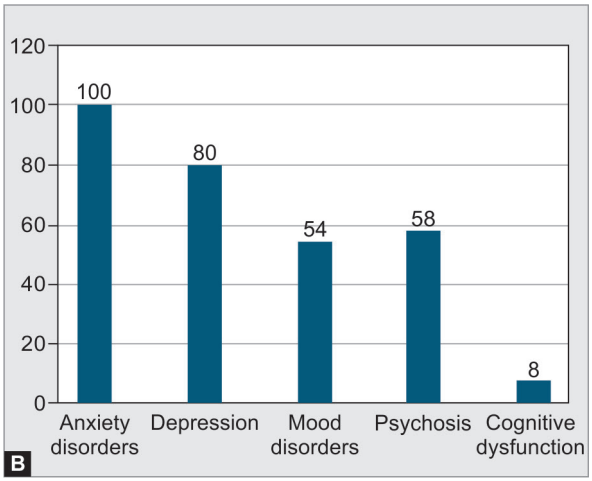

Fig. 1B: Overall prevalence (%) of psychiatric manifestations in our study population

Table 1: SLAM-R scores in SLE patients with anxiety disorders

Parameter	*HAM-A*	*Mean*	*SD*	*p-value*
SLAM-R score	Mild	13.12	6.38	0.002*
	Mild to moderate	12.86	5.21	
	Moderate to severe	22.27	9.07	

Table 2: SLAM-R scores in SLE patients with depression

Parameter	*HDRS*	*Mean*	*SD*	*p-value*
SLAM-R score	Normal	12.78	4.63	0.001*
	Mild	13.00	6.73	
	Moderate	15.40	3.51	
	Severe	24.75	9.57	

*Statistically significant

treatment, and family as well as financial pressure they faced due mostly to poor socioeconomic conditions. We also found that patients who had severe anxiety had a frequent tendency to pass sleepless nights, apprehension of possible complications, and fear of "pain" and "somatic" symptoms. Philip and Bai mentioned in their studies that intermittent flares and remission of various signs and symptoms as well as social stress such as loss of working abilities, decreased income, and limitations in social activities are also major problems.[25,26] The majority of the population in our study were from the middle or poor class and hailing from rural areas, 14% of them were unable to read or write with understanding in any language, meaning SLAM-R for clinically significant disease activity and to initiate therapy was present in 88%(n = 44) which is statistically significant ($p < 0.001$). Anxiety disorders are typically chronic and if without treatment often lead to social and occupational impairment, general disability, and unnecessary utilization of hospital resources.

Mood disorders including depressive features constitute a significant portion (n = 27, 54%) of the population in this study. Bachen et al.[27] found that patients with SLE had higher lifetime rates of certain anxiety disorders and mania. Using MDQ, we have identified those patients who require further evaluation for bipolar disorders and found the majority (n = 11, 40.7%) had major depressive episodes with features of depression. Manic features like "feeling very up, high, elated, or extremely irritable or touchy," "racing thoughts," "decreased need for sleep," "feeling of appetite or drinking, sex, or other pleasurable activities," talking fast about a lot of different things were predominant during acute episodes in all the affected individuals. Contrary to a previous prospective study[28] statistically significant organ damage was present in all the patients with mood disorders.

We found a majority (n = 40, 80%) in our study population had depression who were further assessed using HDRS and found the majority (n = 25, 62.5%) had "mild" depression while four of the patients, classified with "severe" depression (n = 8, 20%), had suicidal thoughts. We immediately referred them to the psychiatrist and monitored a close follow-up. All the patients with clinical depression had statistically significant disease activity as measured on SLAM-R. This further corroborates our findings with previous studies and is on par with the findings of "active" disease manifestations.

Cognitive dysfunction is another common psychiatric manifestation and can be an early soft symptom of neuropsychiatric SLE. In our study, four patients had cognitive dysfunction and two of them had severe cognitive dysfunction and were admitted to the inpatient department. There is mixed consensus regarding the correlation between disease activity, organ damage, and cognitive dysfunction in NPSLE. Conti et al.[29] had shown in their cross-sectional study a correlation between disease activity and cognitive dysfunction whereas Raghunath et al.[30] found a correlation between cognitive dysfunction and organ damage, but no correlation with disease activity in their cross-sectional study. Statistically significant organ damage (SDI > 0) was present among the patients with cognitive dysfunctions in our study ($p < 0.001$). Disease activity measure in our study i.e. SLAM-R had shown statistically significant scores in SLE patients with both "mild" and "severe" cognitive dysfunctions. We hypothesize from our study results that active disease processes may have some role in cognitive dysfunction among NPSLE patients. Further research with active biomarkers and imaging modalities is needed in this prospect to detect early with significant reliability.

Among the isolated patients with a diagnosis of psychosis (n = 29, 58%), the majority (58%) were "mildly ill" (according to BPRS) and predominant symptoms were grandiose delusion and visual and auditory hallucinations. A statistically significant damage was present in most of the patients. The mean BPRS score for damage was 37.05 ± 14.11 and it was statistically significant (p = 0.005). BPRS as a screening tool can significantly contribute to the assessment of overall prognosis in diagnosed NPSLE patients.

Disease activity score (SLAM-R) has shown a positive correlation with all other psychiatric rating scales and implies significant ongoing disease processes may play a role behind the evident psychiatric manifestations. Statistically significant organ damage (SDI > 0) is present in 84% (n = 42) of SLE patients and involves all the concerned domains. So, further assessment of individual systems is required in future follow-ups.

GHQ-28 is found to be a significant predictor for possible psychological distress as well as significant disease activity. It can be easily implemented on an outpatient department basis to rule out early psychological disorders and disease processes. Anxiety

and depression and other psychological disorders may be partially attributed to the long duration of therapy, patient compliance, familial disturbance apart from the chronic disease process. BPRS and GHQ also showed a positive correlation which is further assertive in their implementation as a basic and cost-effective screening tool.

This study was a single center-based study with a very small sample size that warrants careful interpretation of the *p*-value derived in statistical assay. We faced issues starting from a steep decline in overall patient flow, access to basic imaging modalities, and delays in investigations due to the ongoing "nCOVID-19" pandemic. The study was hospital-based; hence, hospital bias could not be completely ruled out. Advanced functional imaging modalities like fMRI facility were not available which can corroborate active disease process and brain activity with given psychiatric manifestations. Remote steroid abuse and subjective bias during assessment with various psychiatric assessment tools could not be completely ruled out.

Conclusion

Psychiatric manifestations are quite prevalent among SLE patients and anxiety disorders are present in all the patients which is followed by depression. These findings, though out of rhythm in comparison to existing prevalence datasets, are a matter of great concern and need to be addressed with proper care. We found SLAM-R scores have been positively correlated with GHQ and BPRS which signifies existing psychiatric manifestations and psychosis severity can be clinical reflector of disease severity. Moreover, the mean BPRS score was statistically significant (37.05 ± 14.11) to correlate with patients having systemic "damage" (SDI > 0). Patients with mood disorders had frequent manic and depressive episodes and four patients classified with "severe depression" had suicidal ideation. Clinical depression rating scale (HDRS) scores are also positively correlated to disease activity index (SLAM-R). All the patients with Cognitive dysfunctions had significant systemic "damage" present and had statistically significant disease activity scores. This extraordinary prevalence of some psychiatric manifestations may be a matter of further justification for future studies with larger sample sizes and improved facilities for functional neuroimaging modalities (e.g., fMRI) for real-time corroboration of data and maximum exclusion of stringent confounding factors limiting our current study.

Clinical Significance

Systemic lupus erythematosus has diverse neuropsychiatric manifestations, of which, psychiatric ones are often neglected, and establishing a temporal relationship with active disease processes after excluding so many confounders (like electrolyte imbalance, drugs, comorbidities, socioeconomic distress, etc.) is quite challenging. In this study, we have tried to exclude some basic factors with the existing tools performed a one-to-one interview process to confirm the diagnosis and used screening questionnaires to further classify each psychiatric manifestation. We found all the patients had at least one psychiatric manifestation and the severity of each manifestation positively correlates with disease activity and damage indices which implies their utility as screening questionnaires for early detection, classification, and prognostication on initial contact with the physician and as monitoring tools for subsequent follow-up. Further studies with greater magnitude can re-improvise the prevalence data and improve the overall calibration of the questionnaires and scoring systems in the studied niche of the population, particularly in Eastern India.

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