DOI: 10.7860/JCDR/2023/65202.18395

Original Article

Internal Medicine Section

Association of HbE Haemoglobinopathy in Patients with Systemic Lupus Erythematosus: A Cross-sectional Study

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ABSTRACT

Introduction: Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease of autoimmune origin that affects multiple systems, with the haematologic system being commonly involved. However, the co-existence of haemoglobinopathies and connective tissue disorders has rarely been investigated, and the available data on this matter are primarily anecdotal.

Aim: To determine the prevalence of Haemoglobin E (HbE) haemoglobinopathy in adult SLE patients and to assess the association of HbE haemoglobinopathy and SLE with disease activity.

Materials and Methods: A hospital-based cross-sectional study was conducted at the Department of General Medicine, Regional Institute of Medical Sciences (RIMS) Hospital, Imphal, Manipur, India, from April 2021 to July 2022. The study included SLE patients diagnosed during the study period who attended the rheumatology Outpatient Department (OPD). The independent variables were age, gender, occupation, religion, and family history, while HbE haemoglobinopathy, Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Red Blood Cell (RBC) count, and Systemic Lupus Activity Measure Revised Index (SLAM-R index) score were the dependent variables. Data were analysed using Statistical Package for Social Sciences (SPSS) version 21.0, with proportions analysed using the Chi-square test and Fisher's-exact test, and means compared using Analysis of Variance (ANOVA) and independent t-test. A p-value of <0.05 was considered significant.

Results: Of the 105 SLE patients included in the study, 93% were females. The majority of participants (36.2%) were in the age group of 21-30 years. Twenty-five patients (23.8%) had HbE haemoglobinopathy. Anaemia and MCV were significantly associated with HbE patients. Among the 25 HbE patients, 24 (96%) had active SLE disease. Among the HbE negative patients, 55 (68.7%) had active disease, while 25 (31.3%) did not have any active disease. Active SLE disease was significantly associated with HbE haemoglobinopathy (p-value=0.002).

Conclusion: The overall prevalence of HbE haemoglobinopathy in SLE patients was found to be 24%. Hb levels and MCV levels were significantly lower in HbE patients. There was a significant association between active SLE disease and HbE haemoglobinopathy.

Keywords: Anaemia, Disease activity, Haemoglobin E, Systemic lupus activity measure revised index score

INTRODUCTION

The SLE is a chronic autoimmune illness characterised by various immunological abnormalities and the production of autoantibodies, which result in widespread inflammation and tissue damage to organs. Globally, the prevalence of SLE ranges from 6.5 to 178.0 per 100,000 people, depending on epidemiological data [1]. Asians and individuals of African ancestry are more likely than Caucasians to develop SLE and experience more severe clinical symptoms of the disease [2]. The clinical presentation and course of the disease vary among populations, indicating the importance of genetics in disease development [2]. In India, the reported prevalence of SLE is 3.2 per 100,000 [3].

Haemoglobin is a tetramer composed of two alpha-like and two beta-like globin chains. Haemoglobinopathies are a group of inherited disorders affecting the globin portion of haemoglobin [4]. HbE is the most common haemoglobin variant in Southeast Asia and Northeast India [5]. It is an abnormal haemoglobin with a single point mutation where glutamic acid is replaced by lysine at position 26 of the beta-globin chain. HbE is the most prevalent abnormal haemoglobin variant in Southeast Asia, Northeast India, and the four different populations of Manipur, India. The Meitei population has the highest incidence of HbE, with 18.207% of individuals possessing HbβE [5]. Among them, 15.81% are heterozygous, 1.917% are homozygous, and 0.48% are compound heterozygous. The incidence of HbE among the Hill Kabui population is 6.67%, with 6.30% being heterozygous and only 0.37% being homozygous. No homozygous individuals have been found in the remaining two populations. The percentage frequencies of heterozygous individuals in the latter are 5.75% and 2.44% among the Kiren and Smite populations, respectively [6].

The SLE is a chronic inflammatory disease of autoimmune origin that affects multiple systems, with the haematologic system being involved in most cases. SLE can cause anaemia through various mechanisms, including haemolytic anaemia. It can also cause thrombocytopenia, especially when associated with antiphospholipid antibody syndrome involving autoantibodies against platelets, glycoprotein IIb/IIIa, or the thrombopoietin receptor [6]. Additionally, some patients with SLE may have another condition that can cause anaemia. It has been found that the prevalence of beta-thalassemia in patients with SLE is lower than that in the general population, but if co-existence occurs, SLE seems to have a more severe course [7].

Haematologic abnormalities are common in SLE, and all three blood cell lines can be affected. Anaemia of chronic disease is the most common type of anaemia in SLE patients, while autoimmune haemolytic anaemia is relatively rare, and severe thrombocytopenia is also rare [8]. The co-existence of haemoglobinopathies and connective tissue disorders has rarely been investigated, and published data on this matter are only anecdotal. Although varying degrees of anaemia are a common finding in SLE, the issue of concomitant haemoglobinopathies has rarely been addressed [7]. SLE associated with beta-thalassemia trait is rare, and concomitant disease tends to exhibit more severe systemic symptoms [9].

Complications appear to be more severe in SLE with beta-thalassemia [7]. The combination of HbE/beta-thalassemia and SLE is even rarer, as reported in cases worldwide [10]. Therefore, the purpose of the present study was to document the prevalence of HbE haemoglobinopathy in SLE and its association with SLE disease activity.

MATERIALS AND METHODS

A hospital-based cross-sectional study was conducted from April 2021 to July 2022 in the Department of General Medicine, Regional Institute of Medical Sciences (RIMS) Hospital, Imphal, Manipur, India. Ethical approval was obtained from the Institutional Research Ethics Board before the study commenced (Ref No. A/206/REB-Comm(SP)/RIMS/2015/699/41/2020).

Inclusion and Exclusion criteria: Patients aged 18 years and above who attended the Medicine OPD, Rheumatology OPD, or were admitted to the medicine ward at RIMS Imphal and diagnosed with SLE during the study period were included. Those who refused to participate were excluded.

Sample size calculation: A sample size of 105 was calculated using the formula: $n=4\times PQ/L^2$ (where P is prevalence, Q= 100-P, and L is the Absolute Allowable error of 6), based on the prevalence of HbE haemoglobin type in the Manipur population as 10.53%, from a study by Singh MR et al., [5].

Study Procedure

A consecutive sampling method was used to recruit participants. The independent variables were age, gender, occupation, religion, and duration of the disease. The dependent variables were HbE haemoglobinopathy, mean corpuscular volume, mean corpuscular haemoglobin, RBC count, and SLAM-R Index score. All eligible patients were informed about the study, and after obtaining informed written consent, a thorough clinical history was taken along with a complete physical examination and investigations. Modified Systemic Lupus International Collaborating Centres (SLICC) Criteria [11] were used to diagnose SLE, where the patient must satisfy four criteria out of 11 clinical criteria and six immunologic criteria, including atleast one clinical criterion and one immunologic criterion. Alternatively, if the patient has biopsy-proven nephritis compatible with SLE and positive Antinuclear Antibody (ANA) or anti double-stranded Deoxyribonucleic Acid (dsDNA) antibodies, they are also considered to have SLE. Disease activity was measured using the SLAM-R Index. The haemoglobin types were screened using high-performance liquid chromatography [12], along with known control samples.

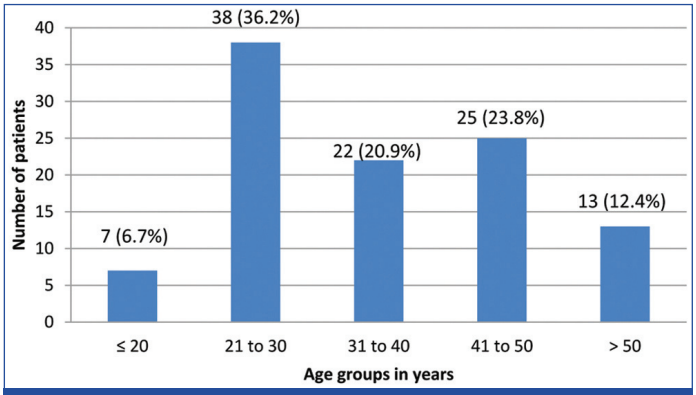
Measurement of disease activity: Disease activity was measured using the SLAM-R Index, which assesses global disease activity within the previous month. It includes 23 clinical manifestations in nine organs/systems and seven laboratory features, with a possible range of 0 to 81. Each organ item may score 0 to 3 points if any of the clinical manifestations were present within the previous month (severity is incorporated into a higher score per item). Most items can score a maximum of three points, while a few items can score a maximum of one point. The laboratory category can score a maximum of 21 points. A score of seven or more was considered indicative of active disease activity [13].

STATISTICAL ANALYSIS

The collected data were entered and analysed using SPSS (IBM) version 21.0. Data summarisation was performed using descriptive statistics such as mean, median, standard deviation, and percentages. Categorical variables were analysed using either the Chi-square test or Fisher's-exact test. A p-value <0.05 was considered statistically significant.

RESULTS

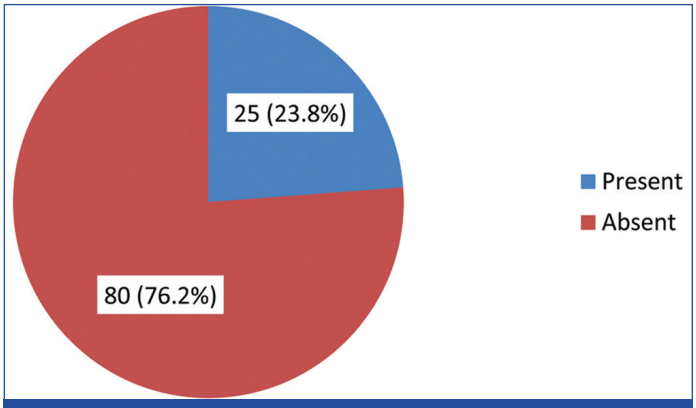
A total of 105 patients with SLE were included in the study. Ninety-eight participants (93%) were females, with a female:male ratio of 14:1. The mean age of the participants was 35.26 years, and the median age was 35 (31-40) years. As shown in [Table/Fig-1], the majority of participants (36.2%) were in the age group of 21-30 years, and only 6.6% were in the age group of 20 years or younger. As shown in [Table/Fig-2], the maximum number of patients (41%) had a duration of SLE between 2.1 to 5 years. The mean duration of SLE was 5.6 years and 59% of patients had a duration of SLE less than five years. The majority of patients were females (93.3%). The majority of the participants in the present study were Hindu (88.6%) and homemakers (73.3%). Twenty-five patients (24%) had HbE haemoglobinopathy, as shown in [Table/Fig-3]. [Table/Fig-4] demonstrates a significant association between MCV (fL) and Hb% with HbE haemoglobinopathy. Hb% and MCV were significantly lower in HbE patients. The mean Hb% was 10.58% in HbE patients



[Table/Fig-1]: Age distribution of the study participants (N=105).

S. No.	Characteristics		No. of patients	Percentage (%)
1.	Gender	Male	7	6.7
		Female	98	93.3
2.	Religion	Hindu	93	88.6
		Christian	9	8.6
		Muslim	3	2.8
3.	Occupation	Homemaker	77	73.3
		Students	24	22.9
		Govt. services	4	3.8
4.	SLE duration (in years)	<1	7	6.7
		1 to 2	12	11.4
		2.1 to 5	43	41.0
		5.1 to 10	29	27.6
		10.1 to 20	14	13.3

[Table/Fig-2]: Distribution of the patients by socio-demographic profile and duration of SLE (N=105).



[Table/Fig-3]: Distribution of patients by presence of HbE haemoglobinopathy (N=105).

and 11.9% in non HbE patients, with a statistically significant difference (p-value=0.02). The mean MCV (fL) was 83 fL in HbE patients and 87.7 fL in non HbE patients, also with a statistically significant difference (p-value <0.001). The mean difference in all other parameters was not statistically significant. Anaemia was significantly associated with HbE positive patients, as shown in [Table/Fig-5]. [Table/Fig-6] shows a significant association between active SLE disease and HbE haemoglobinopathy (based on SLAM-R index score). Out of 25 HbE patients, 24 (96%) had active SLE disease, while among the HbE negative patients, 55 (68.7%) had active disease and 25 (31.3%) did not have any active disease.

Blood parameters	Mean±SD		p-value
	HbE present	HbE absent	
Haemoglobin (%)	10.58±2.02	11.90±1.77	0.02
Total Leucocyte Count (in thousands)	7.38±2.65	7.28±2.95	0.88
Platelet count (in lacs)	5.80±3.62	3.04±5.99	0.15
ESR* (mm)	52±25.4	39.4±32.4	0.08
Mean Corpuscular Volume (fL)	83±5	87.7±5.34	<0.001
Mean Concentration of Haemoglobin (pg)	27.8±2.63	29.29±6.32	0.25
MCHC** (g/dL)	32±1.86	32.45±1.5	0.32

[Table/Fig-4]: Association of Haematological parameters with HbE patients (N=105).
*Erythrocyte sedimentation rate
**Mean corpuscular haemoglobin concentration

Anaemia	No. of patients		p-value
	HbE present	HbE absent	
Present	16	28	0.01
Absent	9	52	
Total	25	80	

[Table/Fig-5]: Association between anaemia and HbE patients (N=105).

Active disease	HbE		p-value
	Present	Absent	
Yes	24	55	0.002
No	1	25	
Total	25	80	

[Table/Fig-6]: Presence of active SLE disease (based on SLAM-R index score) in HbE patients (N=105).

DISCUSSION

The SLE is a systemic autoimmune disease with variable multisystem involvement and heterogeneous clinical features [14]. In the present study, 25 out of 105 patients (23.8%) with SLE were found to have HbE haemoglobinopathy. This prevalence rate is higher than that in the general population of the same areas, which was reported as 10.53% and 11.69% [5,15]. It is also twice the expected prevalence rate of 11.69%. However, a study by Castellino G et al., reported a lower prevalence of beta-thalassemia minor (9.6%) among SLE patients in Italy [7]. This difference in findings suggests the need for further research in this area.

The mean age of the study population in the present study was 35.26 years, with a median age of 35 (31-40) years. In contrast, a study by Castellino G et al., reported a higher mean age of 54 years [7]. In the present study, out of 105 patients, 98 were female and seven were male, accounting for 93% female patients and 7% male patients. This finding of female predominance is consistent with a study by Castellino G et al., where out of 177 SLE patients, 145 were females and 32 were males [7]. The disease activity of SLE was measured using the SLAM-R Index. Among the 25 HbE patients, 24 (96%) had active SLE disease, while one (4%) did not. Among the HbE negative patients, 55 (68.7%) had the disease and 25 (31.3%) did not have any active disease. The association between active SLE disease and HbE haemoglobinopathy was statistically significant. Of the 25 HbE patients, 16 (64%) had anaemia, and the association between anaemia and HbE haemoglobinopathy was statistically significant (p=0.01). Most HbE patients were detected within 10 years of the duration of SLE. The mean duration of SLE was 6.32 years. The difference in age (in years) and duration of SLE (in years) between HbE patients and non HbE patients was not statistically significant.

In the present study, the MCV level was significantly lower in HbE patients. Parameters such as Total Leucocyte Count (TLC), platelet count, Erythrocyte Sedimentation Rate (ESR), Mean Corpuscular Haemoglobin (MCH), and Mean Corpuscular Haemoglobin Concentration (MCHC) did not show significant differences compared to non HbE patients. These variations may be influenced by the duration of the disease and treatment status. Further studies that take into account parameters such as disease duration and treatment status could provide more insight.

Based on these results, it is possible to suggest a relationship between HbE heterozygote subjects and SLE. However, caution is needed before drawing conclusions that HbE trait may have a facilitating effect on the development of SLE. When investigating a small number of patients, the association may be coincidental. Nevertheless, if confirmed, this finding may contribute to a better understanding of the biological aspects of HbE haemoglobinopathy and SLE. The mechanism through which the HbE trait may interfere with the development of SLE remains speculative. The immunological reactivity of HbE heterozygous subjects has not been studied, and the increased prevalence of HbE haemoglobinopathy in SLE patients may be related to genetically determined susceptibility or the influence of environmental factors that alter host susceptibility and facilitate SLE development. Further investigation of HbE heterozygotes with autoimmunity may provide valuable insights into the pathobiology of SLE and HbE haemoglobinopathy.

Limitation(s)

Limitation of the present study include the lack of measurement of anti-dsDNA titre, C3, and C4 complement levels. These factors, which directly affect the disease activity of SLE, may confound the findings of the present study. Additionally, the use of the SLAM-R index, which relies on subjective reporting of symptoms rather than objective documentation, may introduce bias. The index also gives equal weight to mild and severe organ disease activity without considering the significance of the organ involved.

CONCLUSION(S)

The prevalence of HbE haemoglobinopathy in SLE patients was found to be 24%, with a higher proportion of female patients. There was a significant association between anaemia and HbE haemoglobinopathy. Hb levels and MCV levels were also significantly lower in HbE patients. The present study found a significant association between HbE haemoglobinopathy and SLE disease activity using the SLAM-R index, but further research is needed to explore these relationships using other scoring systems and considering other confounding factors.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 11, 2023
- Manual Googling: Jun 17, 2023
- iThenticate Software: Jul 14, 2023 (11%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **May 10, 2023**
Date of Peer Review: **May 23, 2023**
Date of Acceptance: **Jul 26, 2023**
Date of Publishing: **Sep 01, 2023**