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Clinical Implications and Prognostic Value of Lymphopenia in Systemic Lupus Erythematosus : a Study in Madagascar

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Summary

Introduction: *Lymphopenia is a frequent manifestation of systemic lupus erythematosus. The aim was to identify the correlation between lymphopenia and clinical and paraclinical manifestations, and to assess the prognosis of patients in the University Hospitals of Antananarivo.*

Methods: *This was an analytical, retrospective, longitudinal study from January 2010 to January 2021. Lupus patients with lymphopenia <1500/mm3 constituted the exposed group and those with levels ≥1500/mm3 represented the unexposed group. Relative Risk (RR) with a 95% confidence interval (CI) was used. Statistical significance was set at $p \leq 0.05$.*

Results: *During this period, the incidence of lymphopenia was 22.22%. The mean age of lupus patients with lymphopenia was 35.9 years versus 39.9 years for patients without lymphopenia (p=0.050). Lymphopenia was associated with certain visceral disorders, such as cardiovascular (p=0.001), digestive (p=0.041) and hematological (p=0.011) disorders. Lymphopenia twice increased mortality in lupus patients (RR=2 and p=0.016). The SLEDAI score was greater than 6 in 82.5% of lupus patients with lymphopenia vs. 20.7% in the group without lymphopenia. Lymphopenia tripled the risk of flare-ups in lupus patients, and this association was statistically significant.*

Conclusion: *Lymphocyte counts in systemic lupus erythematosus would be useful in assessing disease activity and prognosis of patient survival.*

Keywords: Clinical, Longitudinal study, Systemic lupus erythematosus, Lymphopenia, Prognosis

Introduction

Systemic lupus erythematosus (SLE) is a non-organ-specific autoimmune disease belonging to the connectivitis family [1, 2]. It is a serious condition with a high morbidity and mortality rate compared with the general population [3, 4].

SLE is a systemic disease, with a wide variety of clinical and biological expressions, leading to generalized inflammation and tissue damage [5].

Due to the clinical polymorphism of SLE, classification criteria have been developed. These have evolved over time to improve sensitivity and specificity. Thus, we had the ACR 1982 classification criteria revised in 1997 followed by SLICC 2012 [6, 7]. Lymphopenia, defined as an abnormal decrease in the number of lymphocytes in the blood to less than 1500/mm³, is a frequent hematological manifestation and one of the classification criteria of the ACR 1997 and SLICC 2012 [8, 9]. Lymphopenia increases patients' susceptibility to infections and complicates the management of systemic lupus erythematosus (SLE). It is often involved in disease flares and may be associated with certain severe organ damage [10]. This study aims to assess the frequency, clinical and paraclinical correlates, and prognostic value of lymphopenia in lupus patients in Madagascar.

Methodology

This retrospective, longitudinal, analytical study was carried out in several hospital departments in Antananarivo, including dermatology, rheumatology, nephrology, hepato-gastroenterology, internal medicine, nephrology intensive care and two specialized wards at Joseph Raseta Befelatanana and Joseph Ravoahangy Andrianavalona hospitals. Patients

included were diagnosed according to ACR criteria and had complete medical records. The study period spanned 11 years, from 2010 to 2021. Participants were divided into two groups: those with lymphopenia (lymphocyte count < 1500/mm³) and those without lymphopenia (lymphocyte count ≥ 1500/mm³). Data were collected exhaustively and analyzed using Epi Info software version 3.5.4. Statistical analyses included Chi-square and Fisher Exact tests to compare clinical and paraclinical variables between groups. Patient survival was assessed using the Kaplan-Meier method.

Results

Of the 180 lupus patients included in the study, 40 (22.22%) had lymphopenia. The mean age of patients with lymphopenia was 35.9 years, compared with 39.9 years for those without (p = 0.05). Women accounted for 92.2% of patients, with a male/female sex ratio of 0.08.

Patients with lymphopenia had cardiovascular (25% vs. 9.3%, p = 0.001), digestive (7.5% vs. 1.4%, p = 0.041) and hematological (75% vs. 55%, p = 0.011) disorders significantly more frequently than patients without lymphopenia.

Table 1: Distribution of Sample by Clinical Manifestation

Organ damage	Lymphopenia				p-value
	Yes n=40(%)	No n=140(%)	RR	IC 95%	
Cardiovascular					
Yes	10(25,0)	13(9,3)	2,69	[1,27-5,67]	0,001
No	30(75,0)	127(90,7)			
Dermatological					
Yes	38(95,0)	125(89,3)	1,15	[0,94-1,39]	0,147
No	2(5,0)	15(10,7)			
Digestive					
Yes	3(7,5)	2(1,4)	5,25	[1,10-30,34]	0,041
No	37(92,5)	138(98,6)			
Hématological					
Yes	30(75,0)	77(55,0)	1,20	[1,12-1,39]	0,011
No	10(25,0)	63(45,0)			
Rheumatology					
Yes	28(70,0)	94(67,1)	1,03	[0,87-1,21]	0,373
No	12(30,0)	46(32,9)			
Respiratory					
Yes	6(15,0)	120(85,7)	1,01	[0,87-1,16]	0,444
No	34(85,0)	20(14,3)			
Neurological					
Yes	2(5,0)	11(7,9)	0,96	[0,89-1,05]	0,292
No	38(95,0)	129(92,1)			
Renal					
Yes	20(50,0)	63(45,0)	1,04	[0,89-1,22]	0,290
No	20(50,0)	77(55,0)			

Inflammatory and hematological parameters were also affected: leukopenia (90% vs. 7.9%, p= 0.001), anemia (95% vs. 68%, p = 0.001), and thrombocytopenia (37.5% vs. 10%, p = 0.001) were more frequent in patients with lymphopenia. Immunologically, anti-native DNA antibodies were positive in 100% of patients with lymphopenia, versus 80.6% of patients without lymphopenia (p = 0.005).

Patients with lymphopenia had a doubled risk of mortality compared with those without lymphopenia (30.7% vs. 14.8%, p = 0.016), mainly due to infectious complications. The SLEDAI score, which assesses disease activity, was significantly higher (>6) in patients with lymphopenia (82.5% vs. 20.7%, p = 0.001), indicating an increased risk of disease relapse. Survival analysis revealed a 12-month survival rate of 85% in patients with lymphopenia, versus 90% in those without.

We adopted the Kaplan-Meier method for calculating the probability of survival of lupus patients with and without lymphopenia after diagnosis.

Table 2: In Lupus Patients with Lymphopenia

Interval between diagnosis and death in years	V	C	D	N=V-C	h(t) = (N-D)/N	S(t)
0	40	0	0	40	1	1
6 months	40	0	5	40	0.875	0.875
12 months	35	0	1	35	0.97	0.85
over 12 months	34	0	3	34	0.91	0.775

The 12-month survival rate for lupus patients with lymphopenia was 85%.

Table 3: In Lupus Patients without Lymphopenia

Interval between diagnosis and death in years	V	C	D	N=V-C	h(t) = (N-D)/N	S(t)
0	140	0	0	140	1	1
6 months	140	0	8	140	0.94	0.94
12 months	132	0	6	132	0.95	0.9
over 12 months	126	0	6	126	0.95	0.85

The 12-month survival rate for lupus patients without lymphopenia was 90%.

V : number of subjects alive at the start of the interval

D : number of subjects who died at the start of the interval

C : number of subjects alive at last count, whose participation time ends within the interval = Censorship

N : number of subjects exposed to event risk over the interval H (t): probability of survival or instantaneous survival

S(t) : survival function, estimated by multiplying the instantaneous survivals calculated over all intervals.

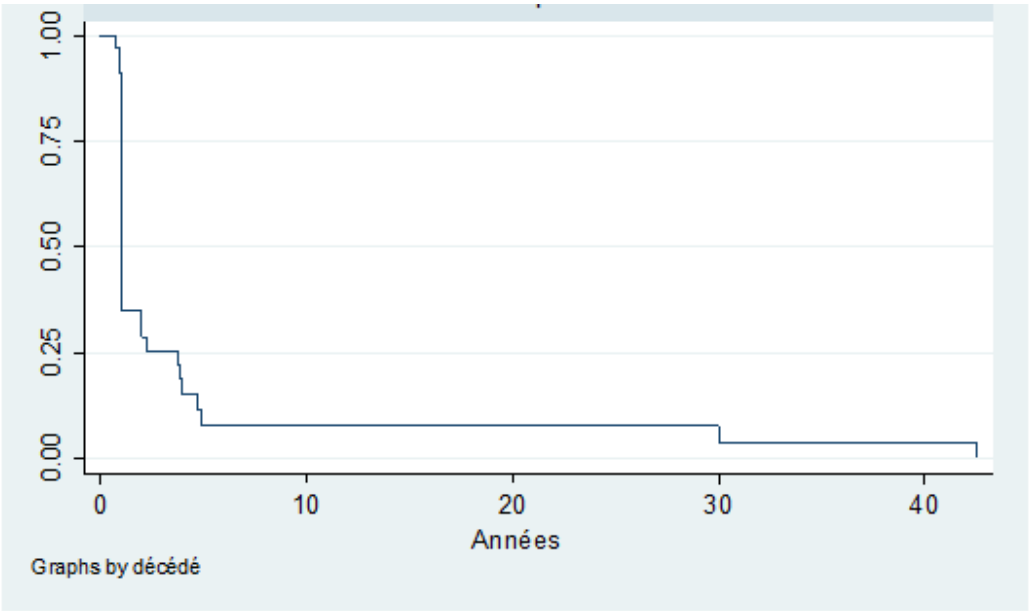

Figure 1: Survivor functions adjusted for with lymphopenia

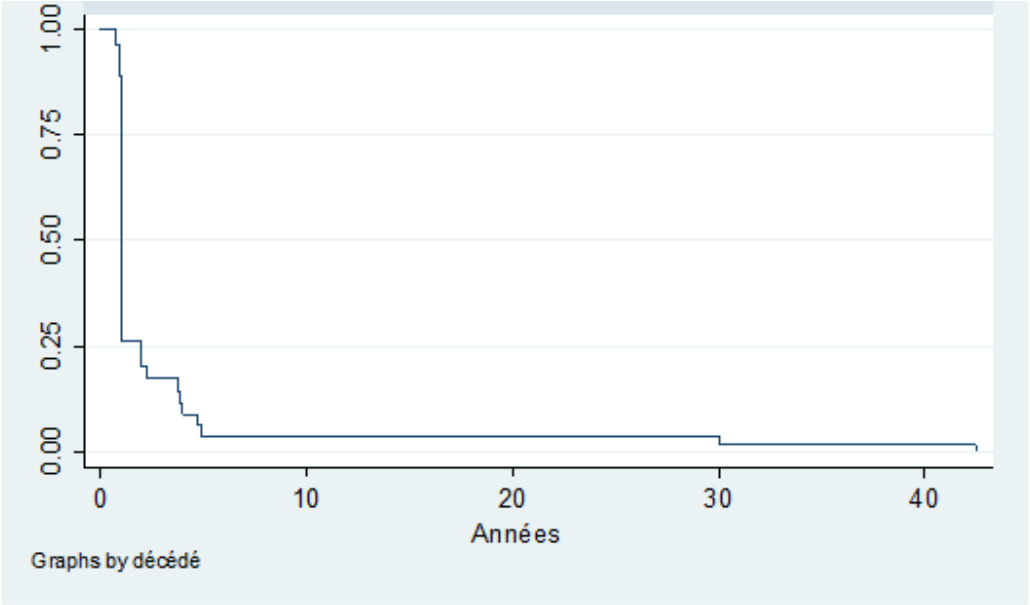

Figure 2: Survivor functions adjusted for without lymphopenia

Discussion

The prevalence of lymphopenia observed in this study (22.22%) is lower than the rates reported in other international studies (45-69.6%), which could be attributed to differences in demographic and genetic characteristics, or the diagnostic criteria used [11, 12]. Some studies have shown that this frequency varies according to age, gender and ethnic origin. Thus, lymphopenia appears to be more frequent in men than in women and occurs more frequently in patients of advanced age [13].

Lymphopenia in SLE is associated with more severe disease activity and severe organ damage, increasing morbidity and mortality. A study from Turkey found that lymphopenia was associated with increased cardiovascular events and organ damage in patients with SLE. This study also observed that patients with lymphopenia had higher rates of hematological damage and cumulative organ damage [14].

A study of a cohort of Egyptian SLE patients revealed that lymphopenia is an independent risk factor for mortality. Patients with lymphopenia had an increased risk of death, notably due to complications such as infections and cardiovascular disease [15]. A meta-analysis consolidated these findings, showing that the presence of lymphopenia in patients with SLE was strongly associated with an increased risk of relapses, underlining the importance of monitoring lymphocyte levels in these patients to prevent disease exacerbations [16].

The results of this study suggest that lymphopenia could serve as an independent prognostic biomarker for SLE, enabling the identification of patients at high risk of relapses and complications. Appropriate therapeutic management, including the administration of corticosteroids and immunosuppressants, is essential to reduce complications and improve patient survival.

Conclusion

SLE remains a complex pathology, associated with significant morbidity, particularly when complicated by lymphopenia. Early identification and targeted management of patients at risk of lymphopenia can improve prognosis and quality of life. This study highlights the importance of monitoring lymphocyte levels in lupus patients in order to adjust therapeutic management and prevent relapses. Further studies are needed to deepen understanding of the underlying mechanisms and optimize management strategies for SLE patients with lymphopenia, particularly in resource-limited settings such as Madagascar.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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