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WORD COUNT 4310
TIME SUBMITTED 16-DEC-2024 01:07PM
PAPER ID 113557062

Words count – 4,310

Thrombosis in systemic lupus erythematous patients: analysis of COMOSLE-Egypt study population

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Abstract:

Introduction: Thrombosis is prevalent in patients with systemic lupus erythematosus (SLE). However, studies focusing on the impact of thrombosis on damage and survival are still insufficient especially in African countries. The aim of the study was to determine the frequency of thrombosis in a group of Egyptian SLE patients and to identify the impact of thrombosis on damage and survival in SLE patients.

Material and methods: This study is an analysis of a retrospective multicenter COMOSLE study. SLE patients with thrombosis were compared to those without thrombosis regarding demographic data, clinical features, laboratory investigations, medications used, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at baseline, Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC) at last visit, and mortality. Risk factors for thrombosis were analyzed.

Results: Out of 902 studied SLE patients; 142 patients (15.7%) were found to have TE along the course of the disease. Arterial and venous thrombosis were significantly associated with damage

risk (OR:2.444, OR:1.072, p<0.001, p<0.001, CI:1.712-2.776, CI:0.7391.405), respectively. Arterial and venous thrombosis were significantly associated with lower survival (HR:2.054, HR:1.663, p=0.015, p=0.03, CI:1.150-3.670, CI:1.051-2.630), respectively. Triple positive antiphospholipid antibodies (aPL abs) were significantly associated with damage (OR:1.205, p value=0.001, CI:0.501-1.908). The 5 years-overall survival in the thrombosis group and those without were 93.8% and 94.9% respectively, while the 10 years-overall survival results were 84.6% and 90.2%, respectively (p=0.001).

Conclusions: Thrombosis, especially the arterial thrombosis, was found to be significantly associated with increased damage risk and lower survival in SLE patients. Triple positive aPL abs were significantly associated with damage risk.

Keywords: Thrombosis, Damage, Survival, Systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic auto-immune illness with uncertain etiology and a rising prevalence worldwide [1]. SLE patients are virtually more prone to thrombosis [2]. When compared to general population, lupus patients have been reported to have up to 25–50 increased risk of thrombosis [3]. Thrombotic events which comprise deep vein thrombosis, stroke and myocardial infarction, strike 30-40% of SLE patients, causing significant morbidity and mortality [4]. Male lupus patients are more likely to develop thrombotic episodes than women [5,6]. Lupus disease per se, has been recognized as an independent risk factor for each of arterial and venous thrombotic disorders [7]. A venous or arterial thrombosis incidence rate has been documented to surpass 10% and 50% respectively in high-risk individuals [8].

Thrombosis may also be a complication of vasculitis, but the exact mechanism by which this occurs remains unclear [9]. SLE-related vasculitis was found in 33.5% [10]. In addition, about 30-50% of lupus patients may harbor antiphospholipid antibodies (APL abs), these abs are considered as one of the major thrombosis risk factors [2,11]. These antibodies frequently have a significant impact on the clinical manifestations and prognosis of lupus disease [12]. A well-recognized linkage between pregnancy comorbidities in SLE patients and thrombotic disorders has been established [13]. Furthermore, thrombosis has been linked to other factors including smoking,

older age at time of SLE diagnosis, shorter disease duration, disease activity and cumulative damage [3,8,14].

Epidemiological studies focusing on the frequency of thrombosis and potential risk factors are still insufficient in Africa and Arab countries, thus we aimed in the current study to record the frequency of thrombosis in a cohort of Egyptian SLE patients, to determine the risk factors for thrombosis in these patients, as well as to identify the impact of thrombosis on damage and survival in SLE patients.

MATERIAL AND METHODS

The current study is an analysis of the population data of a previously published study titled (Comorbidities among Egyptian systemic lupus erythematosus: The COMOSLE-EGYPT study) [15], which is multicenter, retrospective analysis conducted on 902 Egyptian SLE patients attending rheumatology units in four Egyptian university hospitals (Cairo, Beni-Suef, Minia, and Fayoum) in addition to a private center in Fayoum. SLE patients were diagnosed according to ACR classification criteria for SLE [16].

TE is defined as clinical symptoms and signs of vascular occlusion confirmed by investigations [4], presented as one or more arterial or venous thrombosis, causing thrombotic manifestations along the course of SLE. Thrombotic manifestations included arterial and/or venous thrombosis. The following investigations were done whenever indicated to confirm or exclude thrombosis; computerized tomography (CT) brain, magnetic resonance imaging (MRI) brain, magnetic resonance angiography (MRA), magnetic resonance venography (MRV) for thrombotic stroke or dural venous sinus thrombosis, respectively; duplex ultrasound limb arteries or veins for arterial limb thrombosis, deep vein thrombosis (DVT) or superficial thrombophlebitis, respectively; CT angiography abdomen for splenic infarction, hepatic veins, or inferior venae cava; Electrocardiogram, cardiac enzymes, and cardiac catheterization for coronary artery thrombosis, and echocardiography for intracardiac thrombosis; fundal fluorescein angiography for retinal vein thrombosis; CT chest angiography or ventilation/perfusion scan for pulmonary embolism.

According to the presence or absence of thrombosis, patients were divided into two groups: patients with thrombosis and patients without thrombosis. The two groups were compared

regarding: demographic data, clinical features, laboratory investigations, medications used, disease activity measured by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at baseline [17], disease damage measured by Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC) at last visit [18], and mortality.

Statistical analysis: Data management and analysis was performed using Statistical Package for Social Sciences (SPSS) version 25. Numerical data were checked for normality and were statistically described in terms of mean (standard deviation) or median (range) as appropriate. Categorical data were described as numbers and percentages. Comparison between 2 numerical variables was done using Student t-test if normally distributed and Mann-Whitney U test if not normally. When comparing categorical data, Chi square test was performed. Logistic regression analysis was used with Forward LR variable selection method and it included all significant variables on the univariate analyses. It was done using Kaplan-Meier method with comparison between two or more survival curves using log rank test with Bonferroni adjustment when necessary. All statistically significant factors on Kaplan-Meier analysis entered the multivariate Cox regression analysis using forward likelihood-ratio (LR) method for variable selection. Overall survival rates (OS) were calculated from the date of diagnosis to the date of death or last follow-up. Hazard and odds ratios were computed with 95% confidence interval estimates. P-value is always 2-tailed and set significant at <0.05 level.

Bioethical standards

The current study was conducted in accordance with good clinical practice, and was approved by the authors of the original study and by the ethical committee of the faculty of medicine-Cairo University (N-99-2023).

RESULTS

Among the 902 SLE studied patients, there were 832 females (92.2%) and 70 males (7.8%) with a mean age of 32.47±9.25 years, age of onset of 23.38±8.98 years, and median disease duration of 8.0 years (ranging from 0.5-38 years). The prevailing clinical manifestations in the thrombosis group included pulmonary and cardiac manifestations as well as Raynaud's disease (p=0.003, p=0.001 and p=0.015 respectively). Pregnancy loss was also significantly higher in the thrombosis arm (p=0.01). SLE international collaborating clinics damage index (SDI) was higher in the

thrombosis group (p=0.001). Among the laboratory data, statistically significant differences between the two patient groups were found regarding antiphospholipid antibodies separately and collectively. Thrombocytopenia was higher in the thrombosis group, however not reaching statistical significance (p=0.054). A higher occurrence of comorbidities was observed in the thrombosis group (p=0.003), hypertension and dyslipidemia were statistically significantly higher in the thrombosis group (p=0.047 and p=0.025). Antimalarials were received by a higher percentage of patients in the non-thrombosis group and the difference was statistically significant (p<0.001), while patients receiving cyclophosphamide and azathioprine were statistically significantly higher in the thrombosis group (p=0.013, 0.004 respectively) (Table 1).

Among the 902 studied SLE patients, 142 patients (15.7%) were found to have thrombosis either individually or overlapping along the course of the disease. The majority of thrombosis patients (n=121) developed venous thrombosis which represent (13.4%) and the others (n=42) developed arterial thrombosis (4.7%). Secondary antiphospholipid syndrome (APS) was found in 177/681 (26.0 %), one or more positive antiphospholipid antibodies (aPL) were in 326/681 (47.9 %). Single positive aPL (excluding double and triple positive aPL), double positive aPL (excluding triple positive aPL), and triple positive aPL were reported in 178/329 (54.1 %), 109/444 (24.5 %), 39/577 (6.8 %) respectively. The distribution of thrombosis is described in (Table 2).

Regression analysis detected that APS carried about 1.9 times increase in the risk of thrombosis, while there was about 1.1 times increase in the risk of thrombosis associated with having at least one positive aPL antibodies (Table 3).

Thrombosis as overall was associated with about 2.6 times increase in the risk of damage as assessed by SLICC as compared to non-thrombosis, about 2.2 times increase in the risk of damage was associated with arterial thrombosis as compared to non-arterial thrombosis, while about 1.1 times increase in the risk of damage was associated with venous thrombosis as compared to non-venous thrombosis. Triple positivity of aPL abs was associated with about 1.2 times increase in the risk of damage as compared to non-triple positive, unlike single or double positivity (Table 4).

Two times increase in the risk of mortality was associated with thrombosis overall as compared to non-thrombosis, on the other hand about 2.1 times was associated with arterial thrombosis as

compared to non-arterial thrombosis, and about 1.7 times increase was associated with venous thrombosis as compared to non-venous thrombosis. No significant change in the risk of mortality was associated with either single positivity as compared to non-single positivity (p=0.124), double positive as compared to non-double positives (p=0.178), or triple positive as compared to non-triple positive (p=0.939) (Table 5).

A hundred and sixteen out of the studied 902 lupus patients were deceased (12.9%) by the time of data collection. The 5 years-overall survival in the thrombosis group, and those without were 93.8% and 94.9% respectively, while the 10 years-overall survival results were 84.6% and 90.2% respectively (p=0.001) (Fig. 1).

DISCUSSION

Thrombosis remains a major cause of concern in SLE patients, being one of the most common causes of morbidity and mortality [19]. Ethnic differences have been described to play a role in the incidence of thrombosis in patients with SLE [20]. Nevertheless, only a few studies, especially in Arabic and African countries, were conducted addressing the risk factors of thrombosis and their impact on damage index and mortality.

In this study, the prevalence of thrombosis was 15.7%, in accordance with a prevalence of 16% in Hinojosa-Azaola study [3], and slightly higher than the outcome (10.4%) reported by Park et al [4]. Adwan, however, recorded a lower risk of thrombosis in Arab SLE patients despite a higher prevalence of aPL [21].

A comparison between the two patient groups, with and without thrombosis, in the current study revealed statistically significant differences in many clinical and laboratory aspects, which as expected from similar studies were in favor of the thrombosis group [22,23]. Cardiac and pulmonary manifestations as well as livedo reticularis and pregnancy loss were all statistically significantly higher in the thrombosis group of this study, in addition to Raynaud's phenomenon, whose association with venous thrombosis was investigated by Zuk et al [24], with the conclusion that it might be a novel risk factor for venous thrombosis, especially in women. Livedo reticularis has been described as a risk factor for thrombosis especially for arterial thrombosis in APS in a

previous study [25]. In accordance with other studies [26,27], all aPL abs were significantly higher in the thrombosis group. aPL abs were described as the main triggers of thrombosis in patients with SLE, with a frequency of approximately 30–40% [28], and APS was considered a major risk factor for thrombosis in SLE [4], its role in thrombosis has been delineated: Bhoelan et al [29] showed that APS was the main determinant for recurrence risk of SLE-associated venous thromboembolism irrespective of the presence of a provoking factor. In this study, comorbidities in general, dyslipidemia and hypertension in particular, were statistically significantly higher in the thrombosis arm. A disturbed lipid metabolism in SLE patients and its relationship with inflammation and organ damage has been reported by Huang et al [30]. Dyslipidemia in SLE has been associated with disease activity and future cardiovascular events [31]. Our data regarding hypertension, which is recognized as an important contributor not only to organ damage accrual but also to thrombotic events [32], are in accord with Park et al [4], hence, further emphasizing the importance of effective blood pressure monitoring [32]. In discordance with other studies [17, 33], no statistically significant difference was found between the two studied groups of our cohort regarding corticosteroid intake, probably as we did not compare the cumulative doses. A higher mean daily glucocorticoid dose as a clinical predictor of thrombotic events in SLE patients was reported by Park et al. [4]. On the other hand, we observed a significant difference concerning cyclophosphamide and azathioprine intake; being higher in the thrombosis arm, they may be regarded as plausible proxies for SLE activity, which necessitated more intensive treatment.
On the other hand, our results showed that hydroxychloroquine use was significantly higher in the non-thrombosis patient group and was found to be a protective risk factor against the development of thrombosis, thus underlining its value in reducing the risk of arterial and venous thrombosis as observed in other studies [34,35], based on its antiplatelet effect and reduction of APL abs as well as reduction of flares and comorbidity factors as diabetes and hyperlipidemia [36].

Although statistically no significant difference, 31% of the patients with thrombosis had vasculitis compared to 23.8% with vasculitis who did not have thrombosis. The relation between inflammation and thrombosis has been previously addressed, inflammation-induced thrombosis is considered as a feature of systemic autoimmune diseases including SLE [37], inflammation, especially of the vessel wall, is a risk factor for thrombosis. A growing body of evidence suggests that the pathways of inflammation and hemostasis interact extensively [9].

The severity of organ damage has been shown to be a strong predictor of thrombosis [4,33]. Conforming to other studies [38,39], we found damage to be statistically significantly higher in the thrombosis group. Burgos et al [40] described damage accrual to be independently associated with a shorter time to the first thrombotic incidence. The impact of damage accumulation as a strong clinical predictor of thrombotic events has been underscored [4,33], thrombosis could be a contributor to damage accrual or vice versa, damage could be a risk factor for thrombosis. Additionally, recurrent thrombosis is expected to be associated with increased damage index in lupus patients.

Furthermore, we found that triple positivity of aPL abs was associated with increased damage risk. In previous studies, triple-positivity was linked to a higher risk of relapse and obstetrical complications [38, 41]. This contrasts with the results of Demir et al, who stated that triple or double positive aPL profiles were not superior to single LAC positivity in their association with any thrombosis in SLE patients [42]. Clinically significant aPL-profiles, together with older age at diagnosis, and male sex were associated with an increased risk of organ damage accrual during a fifteen-year follow-up [38], and SLE-APS patients exhibited more severe clinical profiles with higher frequencies of major organ involvement, greater damage accrual and higher mortality than SLE patients [39].

Our study showed two times increase in the risk of mortality associated with thrombosis overall, as compared to non-thrombosis. A comparison between mortality rate of hospitalized patients with SLE with and without venous thromboembolism (VTE) studied by Kishore et al showed that VTE in hospitalized patients with SLE was associated with significantly higher inpatient mortality [43]. Gebhart and colleagues [44], who investigated mortality rates and factors affecting them in a prospective observational study, which included LA-positive individuals with or without thrombotic manifestations, concluded that the occurrence of thromboembolic events was associated with an approximately six-fold increased risk of death.

A major strength of our study is that it is one of very few that have included such a large cohort of SLE patients especially in African countries, as an attempt to holistically analyze the impact of

different factors on thrombosis, damage and mortality, and further differentiating thrombosis into overall, arterial and venous, and APL ab into single, double and triple positivity. Nevertheless, the retrospective design of our study is considered among the limitations of this study. The limited number of available beta 2 glycoprotein 1 antibodies either IgG (366) or IgM (372) in relation to the overall studied patients (902) is another drawback. Future prospective studies may provide more data about risk factors of thrombosis in patients with SLE. We also recommend exclusion of infections at the time of aPL antibody determination to avoid potential influence on result interpretation.

CONCLUSIONS

Thrombosis, especially the arterial thrombosis, was found to be significantly associated with increased damage risk and lower survival in SLE patients. Triple positive aPL abs were significantly associated with damage risk.

Disclosures

Conflict of interest: None.

Funding: None.

Ethics approval: The study was approved by the ethical committee of the faculty of medicine-Cairo University (N-99-2023).

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