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**Original Research Article**

# Lupus anticoagulant in systemic lupus erythematosus and its association with complications

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## ABSTRACT

**Background:** The anti-phospholipid antibody which can occur secondary to SLE have a broad spectrum of both thrombotic and non-thrombotic manifestations. Among the three antiphospholipid antibodies, lupus anticoagulant has the strongest association with antiphospholipid syndrome (APS) and increased chance of recurrence of thrombotic events. Hence early screening of lupus anticoagulant is needed.
**Methods:** 72 clinically diagnosed SLE patients were included. The PT, aPTT were done in all patients. The clotting time is assessed by semi-automated coagulation analyser by using dilute russell viper venom time (dRVV) screen and confirm kits. Lupus anticoagulant was considered to be positive if the screen to confirm ratio is ≥1.2. The patients were followed up for a period of 1 year at regular 3 months interval. The various complications like hemolytic anemia, thrombocytopenia, deep vein thrombosis, cerebrovascular accident/transient ischemic attack (CVA/TIA), myocardial infarction, abortions, pulmonary artery hypertension and lupus nephritis were recorded.
**Results:** Lupus anticoagulant was positive in 38.8% among the study group. The most common thrombotic event observed was DVT (16.7%) followed by MI (11.1%) and CVA/TIA (8.3%). There is significant association between lupus anticoagulant positivity with hemolytic anemia, DVT and pulmonary artery hypertension.
**Conclusions:** The lupus anticoagulant has the strongest association with APS in SLE patients and dRVVT is the test of choice in diagnosing APLA. Early recognition of APLA can reduce the risk of thrombotic complications and can prevent further episodes by giving adequate thromboprophylaxis to lupus anticoagulant positive patients.

**Keywords:** Lupus anticoagulant, dRVVT, Anti-phospholipid syndrome, Significant association

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an acquired multiorgan autoimmune disease. Clinical presentation is extremely variable. Females are more affected especially during reproductive years.[1,2] The prevalence of SLE is 6.5 to 178 per 100,000 globally.[3] In India, the prevalence is 3.2 per 100,000.[4] Genetic, immunological, endocrine, and environmental factors influence the loss of immunological tolerance against self-antigens leading to the formation of pathogenic autoantibodies that cause tissue damage.[1,2] Anti-phospholipid syndrome (APS) is characterized by the presence of anti-phospholipid antibodies (APLA) which are directed against phospholipids and the binding proteins. The antiphospholipid antibodies (APLA) include anticardiolipin (aCL), beta-2-glycoprotein and lupus anticoagulant. Lupus anticoagulant constitutes 15-34% of APLA antibodies in SLE.[10] APS provokes both arterial and venous thrombosis as well as pregnancy related complications like abortions and severe preeclampsia. The exact etiology of this is not still clear.[5,6] Genetic risk factors such as coagulation factor mutation , HLA DR7, DR4, DRw53 have been reported in association with APS.[7]

APS can be primary or secondary. Primary APS occurs in the absence of any other autoimmune disease and secondary APS occurs with autoimmune diseases like

SLE. APLA is more prevalent in patients with SLE (50%).[8]

The diagnosis is based on both clinical and laboratory criteria. Deep vein thrombosis of the lower extremities is the most common thrombotic manifestation. Cerebrovascular accidents are the most common arterial thrombotic manifestations followed by myocardial infarction, pulmonary embolism, transient ischemic attacks. There are several clinical manifestations which are not included in the criteria of APS such as thrombocytopenia, hemolytic anemia, cardiac valve disease, renal microangiopathy, livedo reticularis, neurologic disturbances and leg ulcers.[9]

According to a study conducted by Boey et al 31 of the 60 patients with connective tissue disease were found to be lupus anticoagulant positive and 25 of these positive patients had SLE.[11] Thrombotic episodes such as deep vein thrombosis, pulmonary embolism, cerebral thrombosis, renal vein thrombosis and axillary vein thrombosis were recorded in 18 of the 31 patients with lupus anticoagulant positivity.

In patients with SLE who carry APLA and increased risk of thrombotic events, the primary prophylaxis of low dose aspirin is fundamental. Low dose aspirin reduces cardiovascular risk and the occurrence of the first thrombotic events in APL patients.[12,13] Recently, the use of warfarin has been also proposed as primary thromboprophylaxis. Obstetrical complications leads to increased risk of morbidity and mortality for the mother and the fetus. By appropriate management, it is possible to increase the number of successful pregnancies up to 80% of live births.[14] The estimated rate of thrombotic recurrence is about 17% after 5 years and it rises up to 44% after 10 years in patients with a high-risk profile (triple positivity).[15] Early recognition of risk factors including anti-phospholipid antibody in SLE can improve the prognosis and prevent further thrombotic complications if adequate prophylaxis is given. The objective of this study was to determine the proportion of lupus anticoagulant positivity in clinically diagnosed SLE cases and to evaluate its association with various complications.

## METHODS

### *Study design*

This was a descriptive longitudinal study conducted on 72 clinically diagnosed cases of SLE who were diagnosed within 5 years and fulfilled SLICC criteria from rheumatology department, Government Medical College, Kottayam during the study period of 18 months (from November 2019 to April 2021).

The study was approved by the Institutional Review Board of Government Medical College, Kottayam. Patients with bleeding disorders, liver disease and on treatment with heparin were excluded.

Complete blood count with peripheral smear, renal, liver function tests, chest X-ray were collected from the patients. Venous blood samples were collected and double centrifugation was performed in order to obtain platelet poor plasma so that false negative results are avoided. Maximum number of cases were collected within the first 6 months of study period.

The PT, aPTT were done in all patients at the first time of presentation only. The clotting time was assessed by semi-automated coagulation analyser by using dRVV screen and confirm kits. The dRVV screen ratio, confirm ratio and normalized ratio was assessed by the following formulas.

***dRVV screen***

$$\text{Screen ratio} = \frac{\text{Screen clotting time of plasma to be tested}}{\text{Screen clotting time of the reference pool}}$$

***dRVV confirm***

$$\text{Confirm ratio} = \frac{\text{Confirm clotting time of plasma to be tested}}{\text{Confirm clotting time of the reference pool}}$$

$$\text{Normalized ratio} = \frac{\text{Screen ratio}}{\text{Confirm ratio}}$$

The lupus anticoagulant is considered to be positive if the ratio is ≥1.2.

Patients were followed up (at 3 months interval) for a period of 1 year by questionnaire and routine laboratory investigations and the various complications including thrombocytopenia, abortions, deep vein thrombosis, hemolytic anemia, CVA/TIA and lupus nephritis were noted.

The analysis was done using SPSS software (version 26) and the following variables were studied- (a) mean age of the study group; (b) ratio/proportion of gender; (c) frequency/proportion of comorbidities among the study group; (c) frequency/proportion of anemia, thrombocytopenia, leucopenia, pancytopenia among the study group at the time of presentation; (d) frequency/proportion of lupus anticoagulant positivity among the study group; (e) frequency/proportion of baseline hematological parameters in lupus anticoagulant positive and negative study group; (f) frequency/proportion of baseline grading of thrombocytopenia among lupus anticoagulant positive and negative study group; (g) frequency/proportion of various complications among the study group at the end of 3 months, 6 months, 9 months and 12 months; (h) frequency/proportion of different grades of thrombocytopenia among the study group at the end of 3 months, 6 months, 9 months, 12 months; (i)

frequency/proportion of APS among lupus anticoagulant positive study group; and (j) association between lupus anticoagulant positivity and various complications among the study group at the time of presentation and at the end of 12 months.

## RESULTS

Among the study group, the majority of patients belong to the age group 15-30 years (58.4%) (Table 1) and mean age is 30 years. Marked female predominance observed. Female to male ratio is 11:1. Among the 72 patients, Lupus anticoagulant was positive in 28 (38.8%) cases and negative in 44 (61.2%) cases (Figure 1).

On baseline initial investigations, the most common anemia among the study sample is normocytic normochromic anemia (27.8%) followed by microcytic hypochromic (9.7%) followed by hemolytic anemia (6.9%) and 5.6% had grade 3 thrombocytopenia. Leucopenia was found in 26.4% patients and 6.7% had pancytopenia. On evaluating the hematological abnormalities, the complications were more in lupus anticoagulant positive patients (Figure 2).

The various complications were observed on both lupus anticoagulant positive and negative study group at the time of blood sample collection and every 3 months duration for a period of 1 year. At the time of blood sample collection, hemolytic anemia was found to be the most common complications and all of them were positive for lupus anticoagulant.

Lupus nephritis and abortions were the most common complications on all 3 months follow up. The other complications observed were hemolytic anemia, deep vein thrombosis, MI, CVA/TIA and pulmonary artery hypertension. At the end of 12 months 23.6% had lupus nephritis, 21% had abortions, 16.7% had DVT, 12.5% had hemolytic anemia, 11.1% had myocardial infarction, 8.3% had CVA/TIA, 5.5% had pulmonary artery hypertension (Figure 3).

At the end of study period all complications were found to be more in lupus anticoagulant positive patients and there is significant association between lupus anticoagulant positivity with hemolytic anemia (p=0.001), DVT (p=0.005) and pulmonary artery hypertension (p=0.01).

**Table 1: Age distribution among the study sample.**

| Age groups (years) | Frequency | Percentile |
|---|---|---|
| **15-30** | 42 | 58.4 |
| **31-45** | 25 | 34.7 |
| **46-60** | 5 | 6.9 |

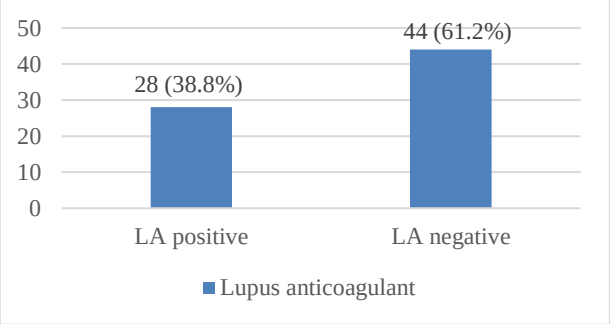


**Figure 1: Proportion of lupus anticoagulant positivity among the study group (n=72).**

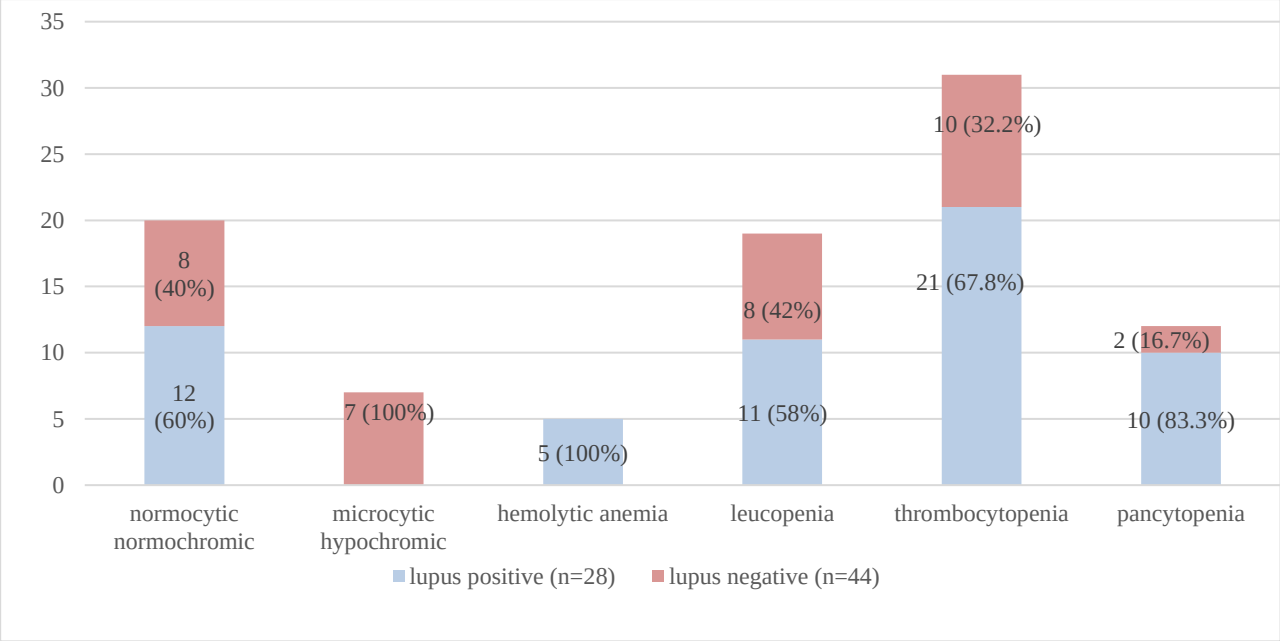


**Figure 2: Distribution of baseline hematological parameters in lupus anticoagulant positive and negative patients.**

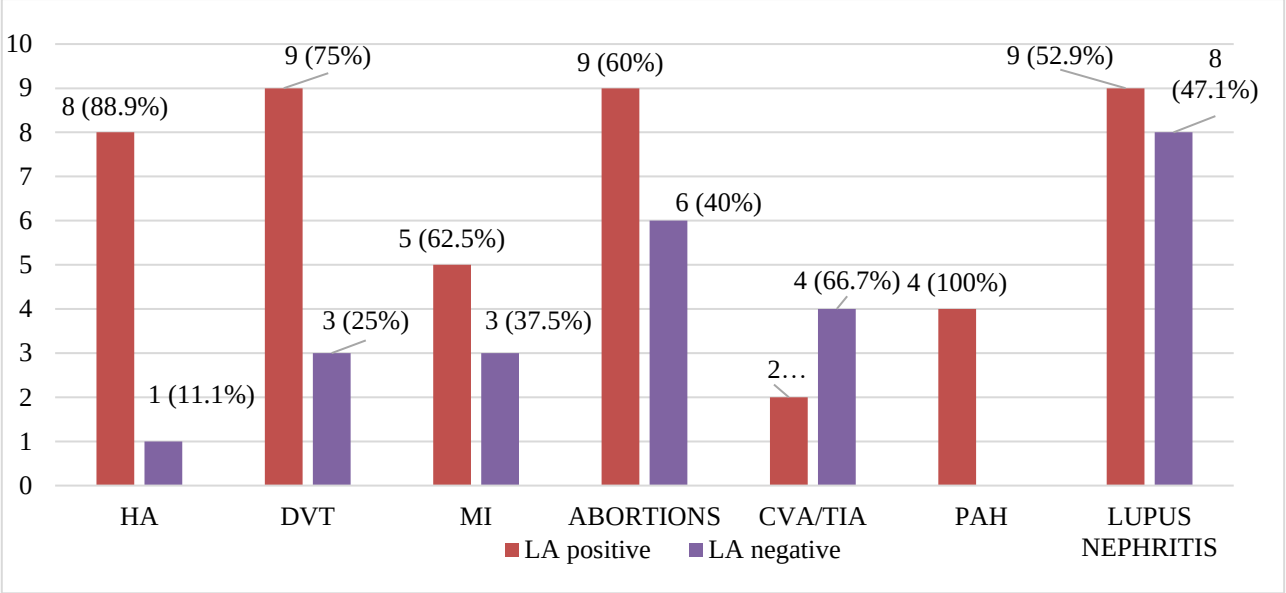


**Figure 3: Distribution of various complications among the study group at the end of 12 months (N=72).**

## DISCUSSION

In the present study females were predominant (91.7%) compared to males and majority of patients were in the age group of 15-30 years. The findings are comparable with the both studies conducted by Hennemann et al and Kishor et al.[16,17] In the present study, the most common baseline hematological manifestation is anemia followed by thrombocytopenia.

32 (44.5%) out of 72 patients show anemia. Out of 32 patients, 20 (27.8%) had normocytic normochromic anemia, 7 (9.8%) had microcytic hypochromic anemia, and 5 (6.9%) patients with hemolytic anemia. The next common manifestation after anemia is thrombocytopenia which is 31(43%) out of 72 patients. 12 (16.6%) out of 72 patients had pancytopenia. 19 (26.3%) had leucopenia. In a study conducted by Bashar et al and Sasidharan et al the most common manifestation is anemia followed by thrombocytopenia.

Normocytic normochromic anemia is the most common anemia seen in both studies.[18,19] Frequent cause of normocytic normochromic anemia is suppressed erythropoiesis or decreased erythropoietin due to renal insufficiency. Antibody induced destruction of red blood cells either by complement mediated or independent has been considered the underlying mechanism for autoimmune hemolytic anemia.

In the present study, test for lupus anticoagulant was only performed. 28 (38.8%) out of 72 patient were lupus anticoagulant positive. 16 (57.1%) out of 28 patients had APS. In a study conducted by Kim et al and Annamma et al prevalence of lupus anticoagulant positivity are 34.1% and 12%.[20,21] The higher positivity in the present study indicates the severity of the disease.

In the present study, the most common thrombotic manifestation was DVT i.e.; 12 (16.6%) patients. Out of that 9 (75%) patients were lupus anticoagulant positive. The next common manifestation was MI followed by CVA and pulmonary artery hypertension. The present study also substantiate that there is significant association with DVT, pulmonary artery hypertension and lupus anticoagulant positivity.

The present study was more comparable with the study by Tarr et al where the most common thrombotic event was DVT followed by CVA, MI and pulmonary artery hypertension.[22]

The p value is significant in all the thrombotic events. In a study by Cervera et al the most common thrombotic event was CVA/ TIA followed by MI, DVT and pulmonary artery hypertension.[23] APLA is the most important risk factor of thrombosis in SLE followed by inflammation, certain thrombophilic factors including drugs. Antiphospholipid antibody syndrome along with chronic inflammation upregulate the procoagulants which will contribute the thrombotic manifestations in SLE.

### *Limitations*

The sample size could not be achieved and Lupus anticoagulant could not be repeated after 12 weeks in majority of the patients due to the COVID pandemic. The study could not explain the efficacy and prognosis of anticoagulant treatment to prevent further recurrence of thrombotic events due to the limited time period of follow up.

## CONCLUSION

The study was done in 72 clinically diagnosed SLE cases

to find out the proportion of lupus anticoagulant positivity in SLE patients and to evaluate its association with various complications in SLE. At the end of 12 months of follow up period, various complications encountered in SLE patients with Lupus anticoagulant positivity include hemolytic anemia, thrombocytopenia, DVT, MI, abortions, pulmonary artery hypertension and lupus nephritis. There is significant association of lupus anticoagulant positivity and the complications hemolytic anemia, DVT and pulmonary artery hypertension. This highlights the possibility of occurrence of thromboembolic phenomena in SLE with the presence of LA. Hence identification of LA positivity in SLE patients at the time of presentation or during follow up is important for early management and prevention of mortality /morbidity due to these complications.

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