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# FREQUENCY OF ANTIPHOSPHOLIPID ANTIBODIES IN LUPUS NEPHRITIS PATIENTS

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**Abstract**

**Objective:**
*To determine the frequency of antiphospholipid antibodies (APLA) in patients with lupus nephritis.*

**Methods:**
*A cross-sectional study was conducted over six months at the Department of Nephrology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, following ethical approval. Ninety-five patients with lupus nephritis, aged 16–60 years, were enrolled using non-probability consecutive sampling. Demographic and clinical data were collected, and antiphospholipid antibody profiles including anticardiolipin (aCL) IgG/IgM, anti-β2 glycoprotein I, and lupus anticoagulant were assessed. Data were analyzed using SPSS version 25, with p-values <0.05 considered statistically significant.*

**Results:**
*Among 95 female patients with lupus nephritis, the mean age was 33.7 ± 9.2 years and 56% tested positive for antiphospholipid antibodies (APLA). Lupus anticoagulant (28.4%) was the most frequent antibody, followed by anticardiolipin (27.4%) and anti-β2GPI (13.7%). APLA positivity was observed in all LN classes, highest in Class IV (70%), but without statistical significance (p = 0.174). Similarly, APLA positivity was comparable across treatment groups (Cyclophosphamide 49%, MMF 61%, Rituximab 59%; p = 0.554). Over 63% reported prior miscarriage.*

**Conclusion:**
*A considerable proportion of lupus nephritis patients exhibited APLA positivity, predominantly lupus anticoagulant and anticardiolipin antibodies, with no significant association with disease class or treatment modality. This highlights the relevance of routine APLA screening in lupus nephritis, especially in patients with obstetric complications.*

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## INTRODUCTION

Antiphospholipid Antibody Syndrome (APS) is an autoimmune multisystemic disorder.

The main feature of the APS is the constant occurrence of the presence of antiphospholipid antibodies (aPLAs) in the context of vascular thrombosis and harmful pregnancy outcomes. It may arise either in primary form, i.e., without any underlying pathogenesis, or in a secondary form, when there is underlying pathogenesis of autoimmune disease. [1, 2]

Antiphospholipid antibodies (aPL) are the most important serological finding in APS. APL can be investigated by laboratory tests such as anti-cardiolipin antibodies (aCL), anti-beta 2 glycoprotein 1 antibodies (anti-beta 2 glycol protein 1) ELISA tests and lupus anticoagulant (LA) [3, 4].

In systemic lupus erythematosus (SLE), patients are more prone to vascular thrombosis and pregnancy morbidity particularly when they have aPL. Nevertheless, not every single SLE and aPL patient develops APS. The occurrence of aPL antibodies is said to reach as high as 30 percent during early stages of SLE [5]. Of the 400 early SLE patients, 154 (38.5%) were found to be positive with any of the aPL antibodies, 127 (31.8%) were found positive to one of the aPL antibodies and 27 (6.8%) were found to have two or more antibodies. Vascular events were much higher among patients with aPL, including doubly/triply positive patients [6-8].

According to reports, different aPL have varying prothrombotic effects. High and medium titers of IgG and IgM are more pathogenic and belong to the Sapporo criteria to diagnose APS [9, 10]. The IgA antibodies are more common amongst European and North American populations and are supposed to be less pathogenic.

Most frequently reported IgA isotype was in a study conducted in Pakistan on the prevalence of aPL antibodies among patients with renal disease and those with suspected APS [11]. An equally greater frequency of IgA aPL epitopes has been identified in South/East Asia.

Lupus nephritis development in patients with systemic lupus erythematosus (SLE) is closely linked to future morbidity and mortality. Very little information is available in our country about the occurrence and nature of aPL antibodies in patients with the lupus nephritis. Most of such patients are young women with risk of poor pregnancy outcomes related to impaired kidney functioning, concomitant intense immunosuppression, and in cases they are accompanied by the aPL antibodies.

A few additional characteristics called non-criteria manifestations of APS, like seizures, livedo reticularis, and Raynaud phenomenon, also are common in SLE, and tend to be more common at first presentation. However, up to now they are not investigated in the local population [12].

The rationale behind the study is to establish the prevalence of antiphospholipid antibodies using patients with proven biopsy lupus nephritis. The role of the presence and variety of antiphospholipid antibodies in lupus nephritis and their clinical value is still unclear because various studies only tried to determine how frequent and what type of antiphospholipid antibodies appear in people who have lupus nephritis. There have been very few studies on the topic in the world and there is also limited data relating to Pakistan on the topic.[13-14].

Since the people of Pakistan are a different population genetically, geographically and in the way of life, the present study is kept aimed at finding the prevalence and types of antiphospholipid antibodies in the patients of lupus nephritis belonging to the indigenous population of Sindh. This study is being carried out in one of the tertiary care hospitals of Karachi.

## MATERIALS AND METHODS

### Study Setting:

This research took place at the Department of Nephrology, Sindh Institute of Urology and Transplantation (SIUT), Karachi.

### Study Duration:

The study was done over 6 months after getting an approval from the Institutional Ethical Review Committee of SIUT and Research Evaluation Unit (REU) of CPSP.

### Study Design

A cross-sectional study.

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**Sample Size**

Sample size was calculated by OpenEpi software with references from a former study by Zhang et al. with APLA positivity 44.7% in patients/with lupus nephritis. Assuming 95% level of confidence and 10% margin of error, the sample size estimated was 95.

**Sampling Technique**

We have used a non-probability consecutive sampling approach to include eligible patients.

**Eligibility Criteria**

**Inclusion Criteria:**

- Patients 16 to 60 years of age
- Patients diagnosed with LN
- Both male and female patients

**Exclusion Criteria:**

- Patients with coexistent autoimmune diseases (such as Rheumatoid Arthritis)
- Patients who had fever in the last 2 weeks
- Pregnant women
- Patients already on anticoagulant therapy

**Data Collection**

This study was conducted after obtaining permission from the Research Evaluation Unit (REU) of the College of Physicians and Surgeons Pakistan (CPSP) and ethical permission (ERC) from SIUT. Demographic and clinical information, including patients' age, gender and duration of diagnosed lupus nephritis were documented on structured proformas after taking written informed consent. Laboratory studies were performed to evaluate antiphospholipid antibody profiles such as anticardiolipin (aCL) IgG and IgM, anti-beta-2 glycoprotein I (anti-β2GPI) antibodies, and lupus anticoagulant (LA). All specimens were obtained under sterile conditions and tested for detectable antibodies.

**Data Analysis**

The data was analyzed by the Statistical Package for Social Sciences (SPSS) version 25. Continuous variables (age, disease duration, APLA levels) were presented in terms of mean with standard deviation. Qualitative data, including gender, and so on (aCL, Anti-β2GPI, LA), were expressed as frequencies and percentages. Stratification for age, sex, duration of disease, and APLA status was used to match for possible confounders. Associations were evaluated using Chi-square test post-stratification. $P<0.05$ was accepted as statistically significant.

**ETHICAL CONSIDERATIONS:**

This study was carried out after approval from the Institutional Ethical Review Committee (IERC) of Sindh Institute of Urology and Transplantation (SIUT) and Research Evaluation Unit (REU) of College of Physician and Surgeons Pakistan (CPSP). Informed consent in writing was obtained before entering the study. All participants' records were kept confidential and all the steps and processes were in accordance with the guideline of ethical committee based on the declaration of aesthetics of Helsinki. Subjects had a right to withdraw from the study at any time point with no effects on their medical management.

**STATISTICS**

Using the SPSS, version 25, data were analyzed. The statistics of continuous variables, i.e. age, disease duration and amount of antiphospholipid antibodies (APLA), were presented in the mean with standard deviation (SD). The categorical data, that is, gender, lupus nephritis (LN) class, and APLA subtypes (anticardiolipin [aCL], anti-B 2 glycoprotein I [anti-B 2GPI], and lupus anticoagulant [LA]), were presented as frequencies and percentages.

Strata were made according to age, sex, disease duration, and APLA status to include all the possible confounding factors. Categorical variables were further tested in terms of their associations using the Chi-square test in post-stratification.

A $p < 0.05$ was taken as significant. Confidence intervals (CI) were given as appropriate to show the accuracy of estimates. All the statistical tests were two-tailed.

Data were presented in figures or charts where appropriate and such a step was without repetition of the results across tables and figures.

**RESULTS**

A total of 95 female patients diagnosed with lupus nephritis were included. The mean age was 33.7 ±

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9.2 years, and urban residence was noted in 50 (52.6%) patients. The mean duration since lupus nephritis diagnosis was 4.8 ± 3.1 months.

**Table 1: Demographic and Clinical Characteristics**

| VARIABLE | MEANS ± S.D/ FREQUENCY (%) |
|---|---|
| Mean Age (years) | 33.7 ± 9.2 |
| Urban Residence | 50 (52.6%) |
| Duration of Disease (months) | 4.8 ± 3.1 |
| Hypertension | 28 (29.5%) |
| Diabetes Mellitus | 14 (14.7%) |
| History of Thrombosis | 20 (21.1%) |
| Serum Creatinine (mg/dL) | 1.10 ± 0.42 |
| Urinary Protein (g/day) | 1.69 ± 0.95 |

**Obstetric History**

Among these patients, 60 (63.2%) reported a history of at least one miscarriage. The mean number of miscarriages was 1.2 ± 0.7.

**Table 2: Antiphospholipid Antibody (APLA) Profile**

| APLA Marker | Positive n (%) | Negative n (%) |
|---|---|---|
| Lupus Anticoagulant (LA) | 27 (28.4%) | 68 (71.6%) |
| Anticardiolipin (aCL) | 26 (27.4%) | 69 (72.6%) |
| Anti-β2GPI | 13 (13.7%) | 82 (86.3%) |

Antiphospholipid antibody (APLA) profiles of the study group are shown in Table 2 with emphasis on the positivity rate for three major APS-related markers. Of the 95 subjects, 28.4% showed positivity for lupus anticoagulant (LA) that was the most commonly detected antibody, whereas Anticardiolipin (aCL) antibodies were slightly less commonly detectable as, 27.4%. Anti-β2GPI antibodies, on the other hand, were less frequent (13.7%). Mean time since last APLA testing was 7.4 ± 2.1 months. Most patients lacked each marker, thus indicating that APS-related antibodies are not ubiquitous, but a significant proportion of the population has serological evidence of APS, predominantly represented by LA and aCL positivity. This has clinical relevance in predicting patients at high risk for thrombosis and adverse pregnancy outcomes.

**Table 3: LN Class vs APLA Status**

| LN Class | APLA Negative | APLA Positive | Total (n) | % APLA Positive |
|---|---|---|---|---|
| Class III | 21 | 19 | 40 | 48.0% |
| Class IV | 8 | 19 | 27 | 70.0% |
| Class V | 13 | 15 | 28 | 54.0% |

**Chi-square p-value = 0.174**

Among the 95 female patients with lupus nephritis, APLA positivity was observed across all histological classes. While Class IV patients showed a higher proportion of APLA positivity (70%) compared to Class III (48%) and Class V (54%), the difference was not statistically significant. Chi-square analysis yielded a p-value of 0.174, indicating no significant association between lupus nephritis class and APLA status.

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**Table 4: Treatment vs APLA Status**

| Treatment | APLA Negative | APLA Positive | Total (n) | % APLA Positive |
|---|---|---|---|---|
| Cyclophosphamide | 18 | 17 | 35 | 49.0% |
| MMF | 11 | 17 | 28 | 61.0% |
| Rituximab | 13 | 19 | 32 | 59.0% |

**Chi-square p-value = 0.554**

The status of APLA is presented for patients in each group in Table 4 Cyclophosphamide, Mycophenolate Mofetil (MMF), and Rituximab. In the 95 patients studied, 53 (56.0%) were positive for APLA and 42 (44.0%) were negative. APLA positivity was found in 49.0% of patients treated with Cyclophosphamide, 61.0% MMF, and 59.0% Rituximab. The proportion of APLA-positive patients in the MMF and Rituximab groups was higher than that in the Cyclophosphamide group, but this was not statistically significant; (p = 0.554, chi-square test), showing no significant relationship between the therapeutic effect and APLA findings. This indicates a relatively even distribution of APLA positivity in the different modalities of treatment, thus does not seem to determine the treatment options in this cohort.

**Figure 1: APLA Positivity by LN Class**

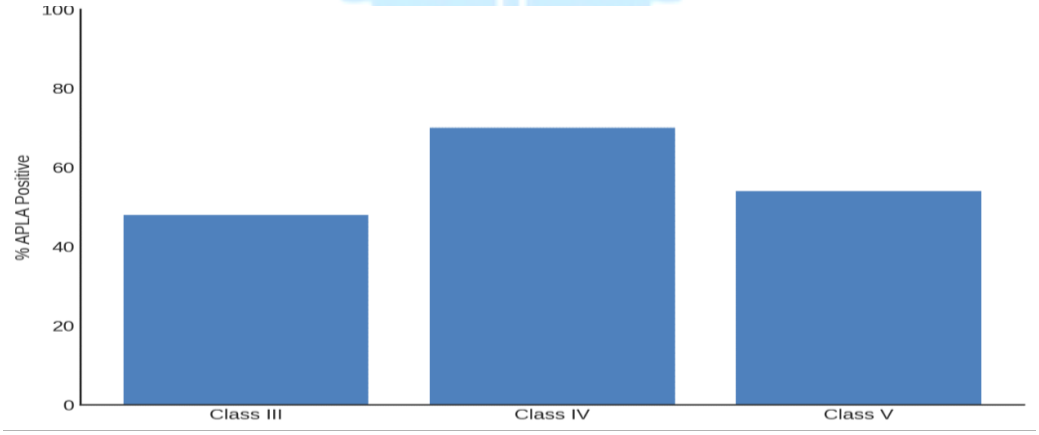


**Figure 2: APLA Positivity by Treatment**

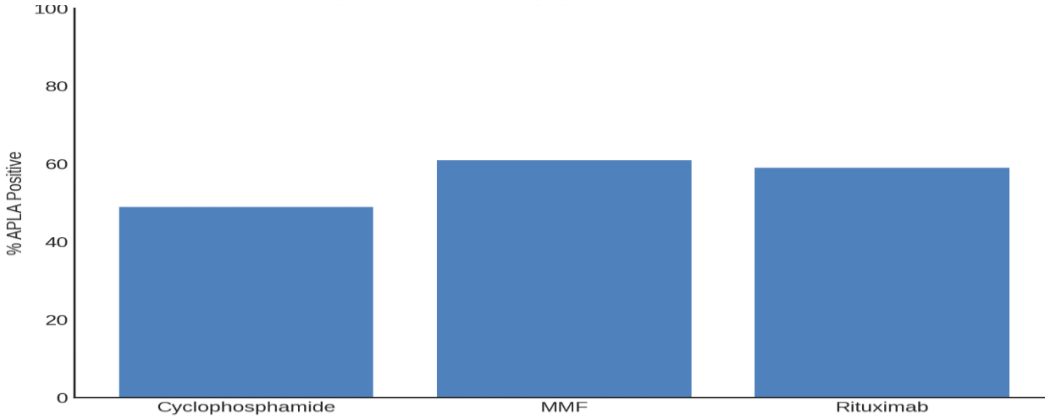


**FIGURE 3: APLA Status in Lupus nephritis patients.**

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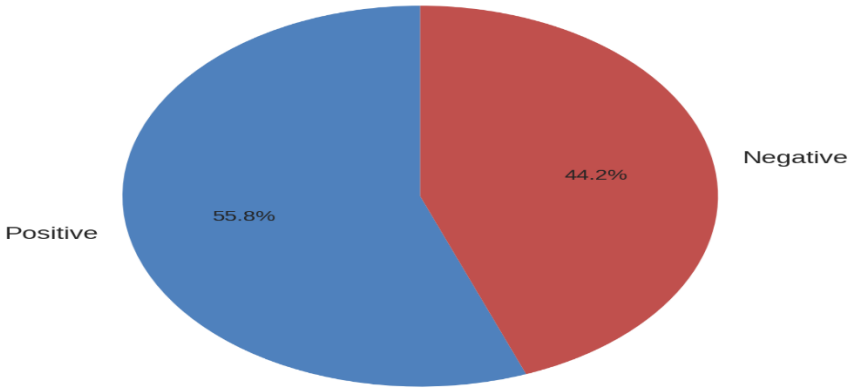


## DISCUSSION

This study describes the serological and clinical characteristics of female lupus nephritis (LN) patients, and analyses the absolute predominance and titer distribution of antiphospholipid antibodies (APLA) and their relationship with histopathological class and treatment regimes.

More than half (56%) of the subjects exhibited APLA positivity, including lupus anticoagulant (LA; 28.4%), anticardiolipin (aCL) (27.4%), and anti-β2 glycoprotein I (anti-β2GPI) (13.7%). These findings corroborate earlier findings of APLA prevalence in SLE but also from their PA, in which LA and aCL frequently present themselves as the prevalent hallmark, in connection not only with thrombotic history but also with obstetric complications [15, 16]. The relatively high proportion of miscarriages (63.2%) in our series is in accordance with the literature, which reports an association between APLA and recurrent pregnancy loss, especially in patients with lupus and positive for antiphospholipid syndrome (APS) [17]. Several investigations have demonstrated the association between APLA positivity and poor pregnancy outcome, and have attributed the cause of the association to placental vessel/thrombosis and complement activation [18].

According to LN class, APLA-positivity was highest in Class IV (70%) but this was not statistically significant. It has previously been reported that the association between LN class and APLA is inconsistent. Some reports show that APLA-positive patients seem to be prone to have worse type of renal lesions, especially thrombocytic renal microangiopathy, and proliferative forms such as class III and IV [19–20]. Other studies, like ours, nevertheless, have not evidenced statistically significant differences in APLA in relation to histological subtypes [21].

There was no significant correlation between the distribution of treatment and APLA status; a slightly higher percentage of patients receiving MMF and Rituximab were APLA positive. These results may echo the clinical practice that dictates the utilization of advanced pneunomodulatory therapy in the presence of more immunologically active or refractory disease such as Rituximab, for which its efficacy in APLA positive lupus nephritis has been investigated [22,23]. Nonetheless, the current existing evidence is still uncertain whether treatment strategies should be based on the APLA status only [24].

Our results support the need to screen for APLA in LN, especially for those patients who have a history of pregnancy loss or thrombotic events. The APLApositive result may not only act as biomarker of risk but may also impact on long-term management and follow up strategies.

This study is subject to several limitations, such as cross-sectional design, small sample size and no follow-up to the response to treatment and pregnancy outcomes. Nevertheless, it offers interesting information on the serological profile of LN patients in our environment.

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## CONCLUSION

In this study of female patients with lupus nephritis, over half demonstrated antiphospholipid antibody (APLA) positivity, with lupus anticoagulant being the most prevalent marker. While Class IV lupus nephritis patients exhibited higher APLA positivity, and patients treated with MMF or Rituximab showed slightly increased rates compared to Cyclophosphamide, these differences were not statistically significant. Notably, a significant proportion had a history of miscarriage, emphasizing the clinical relevance of APLA in obstetric outcomes. These findings underscore the importance of comprehensive APLA profiling in lupus nephritis patients for better risk stratification, particularly for thrombotic and pregnancy-related complications.

**Conflict of Interest:**
None declared.

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