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**Authors and Affiliation:**

Syed Awais Haider Kazmi[1], Qudrat Ullah Malik[2], Bilal Akhlaq[3], Hafsa Arshad[4], Zohaib Akhter[5], Umair Anees[6]

[1-6]Combined Military Hospital Rawalpindi, Pakistan.

[*]**Corresponding Author Email**: awaishaidar@gmail.com



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**Original Article**

# Correlation of Serum Immunoglobulin-E Level with Relapsing Idiopathic Nephrotic Syndrome in Children

Syed Awais Haider Kazmi[1], Qudrat Ullah Malik[2], Bilal Akhlaq[3], Hafsa Arshad[4], Zohaib Akhter[5], Umair Anees[6]
[1-6]Combined Military Hospital Rawalpindi, Pakistan.
[*]**Corresponding Author Email**: awaishaidar@gmail.com

## ABSTRACT

**Objective:** To correlate the relationship between the level of serum immunoglobulin-Ein relapsing idiopathic nephrotic syndrome.

**Methods:** We conducted this case-control study on 50 paediatric patients of both genders suffering from idiopathic nephrotic syndrome, who were aged between 2 and 12 years. Potential participants with a past history of urinary tract infections, non-nephrotic proteinuria, congenital nephrotic syndrome, secondary nephrotic syndrome, nephritic syndrome, and anatomical renal disorders were excluded.Patients were tested for serum Immunoglobulin E level.

**Results:** Among the 50 participants, 29 (58.0%) were males, and 21 (42.0%) were females. 27 (54.0%) reported atopy in family. The mean age of the participants was 8.42 ± 2.81 years. The mean serum urea was5.03 ± 1.33 mmol/L, and serum creatinine levels were 59.24 ± 11.47 µmol/L. The serum IgE levels were negatively correlated ($r = -0.736$, $p<0.001$). Similarly, serum IgE levels were negatively correlated ($r = -0.408$, $p = 0.003$). However, no statistically significant correlation was found among the serum IgE levels, serum urea, serum creatinine, gender, and family history.

**Conclusion:** In children with idiopathic nephrotic syndrome, elevated serum IgE levels are linked to a higher chance of relapse later on.

**Keywords:** Immune response,Children,Nephrotic syndrome, Pediatrics, Relapse, Serum Immunoglobulin E.

## 1. INTRODUCTION

Nephrotic syndrome (NS) is a clinical and pathological condition characterized by significant protein loss in urine, leading to low levels of albumin in the blood (hypoalbuminemia), swelling (edema), and high levels of lipids (hyperlipidemia). Primary nephrotic syndrome accounts for 95% of all cases and is defined by the absence of identifiable secondary causes, such as systemic lupus erythematosus, Henoch-Schönlein purpura, amyloidosis, or HIV. Among these, when no genetic factors can be identified, it is classified as idiopathic nephrotic syndrome (INS).[1]Incidence rates for INS, a prevalent form of glomerular nephropathy in children, vary from 1.15 to 16.9 incidences per 100,000, contingent on nationality and ethnicity.[2]

Remission is defined as negative or trace proteinuria in 3 consecutive first morning urine specimens. Relapse is defined as development of nephrotic range proteinuria in patients who had previously achieved remission.[3] Immunoglobulins are proteins released from B-cells and plasma cells that constitute a vital part of immune system. Dysregulations in immune system have been associated with various diseases and particularly Immunoglobulin E has been found to be associated with atopicailments like asthma, atopic dermatitis, allergic rhinitis, allergic gastroenteritis and with parasitic infections.[4] Recently, data has supported the presence of high levels of Immunoglobulin E in patients with immunoinflammatory disorders like nephrotic syndrome. A number of studies have reported relapse of disease in association with seasonal allergies and atopic diseases and elevated serum IgE concentration in children with NS that rises in the acute phase, declines in remission and again elevates during relapses.[5]

This study was done to ascertain whether having high serum titers of Immunoglobulin E at the time of diagnosis had any relation with developing subsequent relapses in children who did not have any secondary or genetic causes of nephrotic syndrome. This can sensitize the clinicians and caretakers to keep a low threshold of suspecting relapse in children who had high serum IgE levels at the time of diagnosis and can open doors for further research on relation between these two factors particularly role of Anti-Immunoglobulin E therapy to prevent relapses of idiopathic nephrotic syndrome.

## 2. METHODOLOGY

This prospective case-control study was carried out in the Department of Paediatrics at the Combined Military Hospital, Rawalpindi, between January 2024 and June 2024. The study included 28 paediatric patients diagnosed with idiopathic nephrotic syndrome, with informed consent obtained from their parents or legal guardians. Participants were selected through purposive, non-probability, consecutive sampling.The sample size was determined using the OpenEpi calculator, with a 95% significance level, a power of 0.8, and serum IgE levels set at 1150.77 ± 4.61 IU/L for cases and 537.98 ± 52.56 IU/L for controls. Written informed consent was secured from all participants' parents or next of kin. Ethical approval for the study was granted by the Institutional Ethical Committee (Certificate No:304).

All paediatric patients between the ages of 2 and 12 years, of both genders, diagnosed as suffering from idiopathic nephrotic syndromedefined as evidence of nephrotic range proteinuriacausing hypoalbuminemia, oedema and hyperlipidemia without the presence of a known secondary cause or a genetic mutation and having relapse were included for cases while the controls included patients with no history of relapse.Potential participants with a history of secondary causes of a nephrotic syndrome like systemic lupus erythematosus, amyloidosis, hepatitis B/C, Henoch-Schönlein purpura,

diabetes, post-streptococcal glomerulonephritis, or afamily history of nephrotic syndrome were excluded.All patients diagnosed with idiopathic nephrotic syndrome were tested for serum Immunoglobulin levels. They were divided into two groups. The cases which included INS patients with relapse and controls included patients with INS but no relapse. The physical examination and relevant clinical history were recorded. The laboratory investigation included complete blood counts and renal function tests. Additionally, tests were performed to include or exclude patients if the necessary tests had not already been done.

Statistical analysis was conducted using IBM SPSS Statistics (Version 26; IBM Corp., Armonk, USA). Quantitative variables, including patient age, were expressed as mean ± standard deviation, while qualitative variables such as gender and family history of atopy were reported as frequencies and percentages.Group comparisons were performed using the independent samples t-test for quantitative data, whereas categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. Statistical significance was set at $p \leq 0.05$. Additionally, Pearson correlation analysis and receiver operating characteristic (ROC) curve analysis were employed to evaluate associations between variables and determine optimal cut-off values

## 3. RESULTS

This study enrolled 50 children aged 2–12 years, comprising 29 males (58.0%) and 21 females (42.0%). A family history of atopy was reported in 27 participants (54.0%). The mean age was 8.42 ± 2.81 years, with mean serum urea and creatinine levels of 5.03 ± 1.33 mmol/L and 59.24 ± 11.47 µmol/L, respectively. Baseline demographic and clinical characteristics are summarized in Table-I.

**Table-I:Baseline characteristics of sample populations (n=50)**

| Variable | Total Population | Groups | | *p* value |
|---|---|---|---|---|
| | | Cases | Controls | |
| **Gender** | | | | |
| Female | 21 (42.0%) | 11 (44.0%) | 10 (40.0%) | 0.774 |
| Male | 29 (58.0%) | 14 (56.0%) | 15 (60.0%) | |
| **Age (years)** | 8.42 ± 2.81 | 8.80 ± 3.14 | 8.04 ± 2.44 | 0.345 |
| **Family History of Atopy** | | | | |
| Yes | 27 (54.0%) | 18 (72.0%) | 9 (36.0%) | 0.011 |
| No | 23 (46.0%) | 7 (28.0%) | 16 (64.0%) | |
| **Laboratory Parameters** | | | | |
| **Serum Urea** | 5.03 ± 1.33 | 5.31 ± 1.48 | 4.76 ± 1.11 | 0.145 |
| **Serum Creatine** | 59.24 ± 11.47 | 61.76 ± 11.96 | 56.72 ± 10.59 | 0.121 |
| **Hemoglobin** | 10.54 ± 1.67 | 9.74 ± 1.77 | 11.35 ± 1.11 | <0.001 |
| **Serum IgE Levels** | 788.98 ± 260.48 | 978.88 ± ± 194.70 | 599.08 ± 159.65 | <0.001 |

**Table-II:Correlation between serum IgE levels and different clinical and laboratory parameters (n=50)**

| Variable | Correlation co-efficient (r) | p-value |
|---|---|---|
| **Study Groups** | -0.736 | <0.001 |
| **Gender** | 0.089 | 0.537 |
| **Family History** | 0.225 | 0.115 |
| **Serum Urea** | 0.132 | 0.363 |
| **Serum Creatinine** | 0.270 | 0.058 |
| **Serum Hemoglobin** | -0.408 | 0.003 |

Correlation analysis revealed a statistically significant inverse relationship between serum IgE levels and study groups, with a strong negative correlation ($r = -0.736$, $p < 0.001$). A secondary negative association

was also identified (r = -0.408, p = 0.003). In contrast, further analysis demonstrated no significant correlations between IgE levels and other parameters, including serum urea, creatinine, gender distribution, or family history of atopy, as detailed in Table-II.

The ROC analysis identified a serum creatinine cutoff of ≥844.50 µmol/L as predictive of relapse in pediatric idiopathic nephrotic syndrome, demonstrating 64% sensitivity and 80% specificity. As illustrated in Figure 1, the AUC was 0.924 (95% CI: 0.855-0.993; p<0.001), indicating excellent diagnostic accuracy.

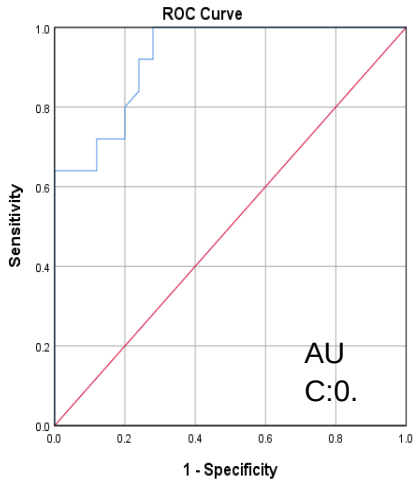


**Figure-1: Receiver operating cure (ROC) for predicting relapse in idiopathic nephrotic syndrome**

## 4. DISCUSSION

As one of the most frequent and clinically challenging renal pathologies in pediatric patients, nephrotic syndrome poses considerable management difficulties due to its relapsing nature, which directly impacts disease morbidity and long-term prognosis. The medical community has extensively researched various prognostic markers that might predict relapse occurrence and severity. In this context, our investigation provides novel evidence linking serum Immunoglobulin E concentrations with INS relapse patterns. Demographic analysis revealed an overall mean patient age of 8.42±2.81 years, with interesting age variations observed between groups - the case cohort averaged 8.80±3.14 years compared to 8.04±2.44 years in controls, suggesting potential age-related considerations in relapse susceptibility. The family history of atopy was reported in 27 (54.0%) patients. It was found to be more prevalent in cases of relapse 18 (72.0%), in accordance with the findings of Ali et al.[7]There were 29 (58.0%) boys and 21 (42.0%) girls signifying the male predominance of the disease. Similarly, a higher proportion of males/ boys were reported to have nephrotic syndromes by other researchers.[6,8]The baseline serum creatinine and serum urea levels in controls and cases showed no statistically significant difference (p = 0.121 and p = 0.145). Hemoglobin levels differed significantly between the study groups (p < 0.001). The mean serum IgE levels in cases were 978.88 ± 194.70 IU/L, and in controls, they were 599.08 ± 159.65 IU/L, with a p-value of less than 0.001.

The idiopathic nephrotic syndrome was found to be associated with raised serum IgE levels and, more specifically, with the steroid-resistant variant. The area under the curve of 0.998 was reported for differentiating cases suffering from Nephrotic syndrome from controls.[9] In coherence with their findings, a cutoff value of 844.50 µmol/L or higher was found to have a sensitivity of 64% and a specificity of 80% for predicting relapse in children with idiopathic nephrotic syndrome. The area under the curve was 0.924 (95% CI: 0.855, 0.993; p < 0.001). Many researchers have reported that serum IgE levels are markedly increased in nephrotic syndrome and its various variants compared to controls.[10,11]The elevated immunoglobulin levels suggest an underlying immune basis pathology in nephrotic syndrome.[11] The patients suffering from INS with raised IgE levels were found to have poor disease outcomes and frequent relapses.[13] In this research, we also found markedly elevated serum IgE levels compared to patients

suffering from INS but who had no relapse of the INS.

In a study by Sadat et al., the patients suffering from Nephrotic syndrome and were steroid-independent and had higher serum IgE levels had more frequent relapses compared to the group of steroid-dependent patients.[14] Moreover, the underlying immune response in the pathogenesis has been widely studied and explains the elevated titers of immunoglobulins in idiopathic nephrotic syndrome.[15]These postulated and studied mechanisms plausibly explain the elevated immunoglobulin levels in both controls and cases in this study. Elevated IgE titers were identified as an independent factor for relapse and remission in minimal change disease, with higher titers associated with early relapses.[16]However, another study found no statistically significant difference between steroid-resistant and sensitive variants of nephrotic syndrome, but levels were elevated in those with relapses of the disease than those in the remission phase of the disease.[17]Many other studies have also reported the role of IgE in nephrotic syndrome and associated relapses.[18,19,20]

Our study had a comparatively shorter follow-up period of 1 year, of which few weeks to months were spent on induction therapy to achieve remission; it is unclear whether the association of Serum Immunoglobulin E with relapse of nephrotic syndrome holds true in longer periods of time, which may serve as the focus of future research. Our study did not focus on the compliance with treatment after discharge from hospital and we labelled remission on the basis of urine dipstick data as provided by parents in few cases who monitored proteinuria at their homes, while other cases were confirmed from laboratory reports.Therefore, the results may not be generalizable to the general population. Further multi-center study on a more diverse population is suggested before conclusions can be applied to the general population.

## 5. CONCLUSION

Idiopathic nephrotic syndrome is arenal disorderswhich relapse carries significant morbidity and mortality and brings great distress to the parents and children. Serum Immunoglobulin E levels can serve as a predictor of the risk and future relapse, and may even forecast the likelihood of frequent or infrequent relapse. Future research should focus on confirming this finding in a larger population over a longer period and exploring the possibility of preventing or treating disease relapse with anti-immunoglobulin E therapy.

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