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Are Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) Predictors of Steroid Therapy in Children with Nephrotic Syndrome?

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Abstract

Background: Nephrotic syndrome (NS) is the most common pediatric chronic kidney disease characterized by massive proteinuria, hypoalbuminemia, edema, and hyperlipidemia. Corticosteroids, as the mainstay of treatment, resolve symptoms in most patients. However, some patients experience a relapsing-remitting course. Currently, there is no specific biomarker for the prediction of steroid response in patients with NS. The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are inexpensive, readily accessible parameters that are proved to be related to the inflammatory state in many disorders.

Method: We evaluated NLR and PLR ratios before and after steroid therapy in 50 pediatric patients with NS in a single pediatric referral center. Data analysis was carried out using SPSS software and the significance level was considered as 0.05.

Results: Medical response to steroid was compatible with steroid-dependent (SD) nephrotic syndrome (NS) in 30% (n=15), steroid-resistant (SR) NS in 12% (n=6), steroid-sensitive (SS) NS in 36% (n=18), and frequently relapsing (FR) NS in 22% (n=11). Fourteen patients (29.2%) did not experience recurrence. Before and after steroid therapy, the mean PLRs were 10.9 and 11.7 and the mean NLRs were 1.9 and 2.2, respectively, which were not statistically different (P>0.05).

Conclusion: We do not recommend NLR and PLR as predictors of steroid response in pediatric patients with NS.

Key Words: Children, Nephrotic syndrome, Neutrophil lymphocyte ratio, Platelet lymphocyte ratio.

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1- INTRODUCTION

Nephrotic syndrome (NS) is the most common pediatric chronic kidney disease (CKD), with an incidence of 2-7 new patients per 100000 children (1). NS is clinically characterized by massive proteinuria (proteinuria>40 mg/h/m2 or ≥ 1000 mg/m2/day or urine protein creatinine ratio ≥ 2 mg/mg or 3+ on urine dipstick), hypoalbuminemia (< 3.5 g/dL), edema, and hyperlipidemia (2). The mainstay of treatment is corticosteroids which resolve symptoms within six weeks in 85-90% of patients (3). However, more than 50% of patients experience a relapsing-remitting course of the disease and require administration of a second line steroid-sparing immunosuppressives (calcineurin inhibitors, mycophenolate mofetil, etc.) (4).

Currently, no specific laboratory indicator of NS response to steroids is available, and clinically, the development of hypertension, hematuria, glomerular filtration rate (GFR) decline, detection of hereditary podocytopathy, and early relapse episode are shown to be associated with poor outcomes (5-7).

The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are inexpensive, readily accessible parameters that are proved to be related to conventional markers of inflammation (8).

The primary object of this study was to investigate alterations of NLR and PLR in variable types of NS in order to evaluate their eligibility to be used as predictors of steroid therapy in affected patients.

2- MATERIAL AND METHODS

This observational cross-sectional study was performed in a single pediatric referral center, Mofid Children's Hospital, from 2019 to 2020, on randomly selected children previously diagnosed with nephrotic syndrome.

Enrolled patients were registered participants in "Pediatric Nephrotic Syndrome Registry" in the Pediatric Nephrology Research Center, Shahid Beheshti University of Medical Sciences.

Nephrotic syndrome criteria were considered as: massive proteinuria (proteinuria>40 mg/h/m2 or ≥ 1000 mg/m2/day or urine protein creatinine ratio ≥ 2 mg/mg or 3+ on urine dipstick), hypoalbuminemia (< 3.5 g/dL), edema, and hyperlipidemia

Nephrotic syndrome was categorized as steroid-resistant (SRNS), steroid-sensitive (SSNS), steroid-dependent (SDNS) or frequently relapsing (FRNS) based on the clinical course and at least 6 months of follow up.

FRNS was defined as SSNS with ≥ 2 relapses within 6 months, or ≥ 4 relapses within a year. SDNS was defined as SSNS with ≥ 2 consecutive relapses during tapering or within two weeks of steroid discontinuation (1). The proportion of neutrophil to lymphocyte and that of platelet to lymphocyte were calculated based on the routine blood test results. A questionnaire was developed and demographic, clinical, and laboratory data before and after steroid therapy were gathered.

Personal data of the patients remained confidential in this study and the questionnaires were filled in anonymously. The study was approved prior to the administration by the ethics committee of the faculty of medicine in Shahid Beheshti University of Medical Sciences.

2-1. Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1. new diagnosis of nephrotic syndrome. 2. Patient's age ranges between 1 to 16 years. 3. Fulfillment of nephrotic syndrome criteria. 4. Idiopathic/primary etiology of nephrotic syndrome. The exclusion criteria included: 1. Congenital or infantile

nephrotic syndrome. 2. Biopsy indication at the very early stage of the disease. 3. Incomplete clinical and laboratory data. 3. Presence of other comorbidities.

2-2. Data analysis

Once the data were collected, data analysis was carried out by means of SPSS software (Version 25, Chicago, IL). Mean and Standard Deviation were used for describing the quantitative data, and percentage and frequency for the qualitative data. Statistical tests adopted were Kolmogorov–Smirnov test, Chi-square Test, Paired T-Test, and ANOVA. The significance level was considered as 0.05.

3- RESULTS

Overall, 50 patients [60% (n=30) male and 40% (n=20) female] were enrolled in the study. The mean (± standard deviation (SD)) age of patients at the time of the study was 7.2 (± 4.3) years. The mean weight and height of patients studied were 26.4 kilograms and 110.4 centimeters, respectively.

Family history was non-contributory in most patients and three (6%) patients reported a history of renal disorders in the family. A history of hypertension was found in 12% of the patients (n=6, 12%).

Nephrotic syndrome started at childhood in 92% (n=46) of patients and in 8% (n=4) was present at birth. The mean duration of disease follow-up was 3.6 years.

The genetic test was available in one patient, the result of which was NPHS2 (Congenital Nephrotic Syndrome with Podocin mutation).

Kidney biopsy was performed in five cases, comprising two cases of MCD (Minimal Change Disease), one case of FSGS (Focal segmental Glomerulosclerosis), and two non-conclusive cases due to the insufficient data. Medical response to steroids was compatible with SDNS in 30% (n=15), SRNS in 12% (n=6), SSNS in 36% (n=18), and FRNS in 22% (n=11). Fourteen patients (29.2%) did not experience recurrence.

The main treatment was prednisolone, which was the only medication used in 62% (n=31) of the cases. In other cases, rituximab (n=6, 12%), cyclosporine (n=4, 8%), 6% (n=3) with levamisole, and cyclophosphamide (n=1, 2%) were used as second-line immunosuppression. Two patients (4%) were not on medications. In 48% (n=24) of the patients, non-steroidal medications were also consumed.

Five patients (10%) required dialysis, including hemodialysis (n=1), peritoneal dialysis (n=3), a combination of the two types (n=1). In two patients (4%), kidney transplantation was performed. A summary of laboratory findings is presented in **Table 1** and **Table 2**.

Gross Hematuria was positive in 4% of the studied patients (2 out of 50). The mean amount of proteinuria (2.6 (±1.4) vs. 1.5 (±1.4)) and albumin (2.4 (±0.9) vs. 3.0 (±0.9)) in two measurements, carried out prior to and after the treatment, displayed a significant difference (P=0.001). The observed initial and final amounts of leukocytes (9.6 (±3.7) vs. 9.5 (±4.4)), RBC (red blood cells) (4.4 (±1.0) vs. 4.4 (±0.9)), platelet (358 (±143) vs. 363 (±147)), neutrophil percentile (52.5 (±17.5) vs. 53.7 (±19.0)), lymphocyte percentile (40.7 (±17.3) vs. 41.0 (±18.5)), hemoglobin (14.3 (±17.8) vs. 11.8(±2.5)), hematuria (2.2 (±2.1) vs. 1.6 (±1.5)), urea (2.1 (±1.7) vs. 1.6 (±1.2)), and creatinine (0.8 (±0.8) vs. 0.7 (±0.8)) of the patients did not show significant differences. (P>0.05). Before and after steroid therapy, the mean (±SD) PLRs were 10.9 (±7.6) and 11.7 (±9.4), and the mean NLRs were 1.9 (±1.5) and 2.1 (±2.4), respectively (P>0.05).

Table-1: Summary of laboratory findings in 50 patients with Nephrotic syndrome

No.	Item	Value
1	The mean (± SD) of sodium (meq/L)	137.9 (± 0.41)
2	The mean (± SD) of potassium (meq/L)	4.07 (± 0.08)
3	The mean (± SD) of Calcium (meq/L)	8.59 (± 0.22)
4	The mean (± SD) of Phosphorus (meq/L)	4.85 (± 0.19)
5	The mean (± SD) of Complement 3 (g/L)	135.17 (± 9.31)
6	The mean (± SD) of Complement 4 (g/L)	26.66 (± 2)
7	The mean (± SD) of Prothrombin Time (sec)	12.31 (± 0.17)
8	The mean (± SD) of Partial Thromboplastin Time (sec)	32.08 (± 1.76)
9	The mean (± SD) of International Normalized Ratio	1.04 (± 0.03)
10	The mean (± SD) of Triglyceride (mmol/L)	331.4 (±37.5)
11	The mean (± SD) of Cholesterol (mmol/L)	319.1 (±18.4)

Table-2: Laboratory findings before and after steroid therapy

Parameters		SDNS (Mean,SD)	SRNS (Mean,SD)	SSNS (Mean,SD)	FRNS (Mean,SD)
WBC	Initial	8.8 (±2.6)	11.4 (±5.6)	9.2 (±3.2)	10.6 (±3.9)
	Final (×103 cell/uL)	8.3 (±2.5)	11.1 (±5.2)	7.9 (±1.9)	12.1 (±6.5)
RBC	Initial	4.5 (±1.1)	3.7 (±1.04)	4.4 (±0.7)	4.9 (±0.6)
	Final (×106/ul)	4.5 (±1.03)	3.9 (±1.2)	4.3 (±0.8)	4.7 (±0.3)
Hb	Initial	12.5 (±1.9)	10.08 (±3.01)	18.4 (±26.7)	11.1 (±4.9)
	Final (gr/dL)	11.1 (±2.7)	10.6 (±3.3)	12.3 (±2.3)	12.8 (±1.5)
Plt	Initial	365.8 (±111.2)	237.6 (±126.4)	378.8 (±139.3)	439.8 (±168.6)
	Final (×103/ul)	353.7 (±121.8)	285 (±154.8)	354.1 (±118.05)	420.5 (±184.4)
PMN	Initial	51.3 (±13.9)	53.08 (±16.6)	50.1 (±19.7)	55.8 (±19.9)
	Final (% of WBC)	52.4 (±14)	52.9 (±22.8)	51.9 (±25.07)	57.9 (±16.4)
Lymph	Initial	42.2 (±13.7)	39.05 (±13.3)	44.1 (±19.5)	36.8 (±19.7)
	Final (% of WBC)	41.6 (±10.3)	35.3 (±19.8)	42.5 (±24.3)	42.02 (±19.4)
PLR	Initial	10.1 (±7.07)	6.3 (±3.1)	10.8 (±6.9)	15.9 (±10.4)
	Final	9.7 (±6.4)	13.2 (±13.07)	12.9 (±10.05)	12.1 (±9.8)
NLR	Initial	1.4 (±1.1)	1.6 (±0.9)	1.8 (±1.8)	2.2 (±1.8)
	Final	1.4 (±0.8)	2.9 (±4.09)	2.7 (±3.2)	1.8 (±1.3)

SDNS; steroid-dependent nephrotic syndrome, SRNS; steroid-resistant nephrotic syndrome, SSNS; steroid-sensitive nephrotic syndrome, FRNS; frequently relapsing nephrotic syndrome, WBC; white blood cell, RBC; red blood cell, Hb; hemoglobin, Plt; platelet, PMN; polymorphonuclear cells, Lymph; lymphocytes, PLR; platelet to lymphocyte ratio, NLR; neutrophil to lymphocyte ratio.

4- DISCUSSION

Currently, there is no specific biomarker for the prediction of steroid response in patients with NS. Proinflammatory cytokines such as interleukin (IL)-1β, IL-6, and IL-8 are shown to be significantly higher in pediatric patients with SSNS compared to SRNS and are suggested to be used as indicators of steroid response (9). However, in a study by Roca et al. carried out on 101 NS patients (20% of which were pediatric) significantly higher levels

of IL-6, haptoglobin, and hemopexin were reported in 27 patients with SRNS compared to 50 patients with SSNS (10), and, another study detected similar levels of IL1β, interferon-γ, and IL-4 in the SSNS and SRNS patients and during the remission and relapse of the disease (11). These discrepancies between cytokine levels and steroid response may be due to variability in the type of nephrotic syndrome, the age range of the population study, and different stages of the disease, acting as confounding factors. Yet, evaluation of cytokine serum level is not applicable in all settings and is not routinely performed in patients with NS.

Measurement of NLR and PLR ratios is cost-effective and practically performed in all patients with NS, making them potential alternatives for other costlier inflammatory biomarkers. Since the NLR and PLR are ratios between two serum parameters, any alteration in either neutrophils, lymphocytes, or platelets will affect NLR and PLR (12). They have been demonstrated to be related to the inflammatory status in different disorders including cancer, cirrhosis, acute coronary syndrome, carotid atherosclerosis, antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis, and pneumonia (13-15).

In renal disorders, high NLR is associated with the worsening of renal function in CKD, while NLR>1.5 and NLR>3 are linked to early-stage and advanced CKD, respectively (14). NLR is also introduced as a marker with prognostic value for the presence and degree of proteinuria in CKD (16). In addition, NLR is suggested as a screening tool to detect diabetic nephropathy at an earlier stage (17) and also can be used to determine the degree of diabetic nephropathy (8).

The association between NLR and PLR and nephritic syndrome characteristics has been recently investigated. Toraman et al. evaluated fifty-four adult patients with rapidly progressive glomerulonephritis (RPGN) and found that NLR could predict mortality in patients with RPGN and PLR can be an indicator of disease severity in the acute phase of crescentic glomerulonephritis (18).

Another study by Tsai analyzed 99 adult patients with renal biopsy-confirmed idiopathic membranous nephropathy and recognized that NLR>3.34 (hazard ratio (HR) =3.30, $p<0.001$) and PLR>14.48 (HR=2.54, $p=0.003$) are correlated with poor renal outcomes (13).

4-1. Limitations of the study

The authors recognize the limitations associated with this study. There was no homogeneity among the samples of the study in terms of NS subtype and also the administration of immunosuppressives other than corticosteroids. Furthermore, the single-center nature and the small number of enrolled patients limit generalizability. Despite these limitations, the current study is one of the first studies evaluating the association between the NLR/PLR and steroid response in NS patients. Further prospective studies are required with a higher number of patients and distinct subgroups of NS and stratification of the NLR and PLR results according to the remission and relapse states to better elucidate the predictor likeliness of these parameters.

5- CONCLUSION

In this study, we did not find any significant correlation between NLR/PLR ratios and NS categorized based on the response to steroid therapy; therefore, we do not recommend NLR and PLR as predictors of steroid response.

6- ETHICS CONSIDERATIONS

This study was performed according to the Helsinki Declaration and was approved by the Ethical Committee of the Shahid Beheshti University of Medical Sciences. Informed consent was obtained

from the patients and their parents prior to being included in the study.

7- DECLARATIONS OF INTEREST

None.

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