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ORIGINAL ARTICLE

Coagulopathy in Nephrotic Syndrome at Different Disease States: Single Center Experience

Seham Mohammed Ibrahim Ramadan [1], Mohammed Mohammed Abdelsalam Gomaa [1], Ahmed Mokhtar Ahmed Ibrahim [3], Enas Othman Khaled ben Khaled [2], Dalia Gameil[1]
[1] Pediatrics Department, Faculty of Medicine, Zagazig University, Egypt
[2] Pediatrics Department, Faculty of Medicine, Tripoli University, Libya
[3] Clinical Pathology, Faculty of Medicine, Zagazig University, Egypt

Corresponding author:
Enas Othman Khaled ben Khaled

Email:
enasothman60@gmail.com

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ABSTRACT

Background: Nephrotic syndrome is a prevalent glomerular condition that is characterized by edema, hypoalbuminemia, hyperlipidemia, and severe proteinuria. Proteinuria leading to loss of important plasma proteins likes fibrinogen, protein C, S and AT III. As a result, the vascular system is more susceptible to hypercoagulability and plasma anticoagulant factor levels are lower. This study aimed to evaluate the effect of nephrotic syndrome on coagulation status. Methods: This case-control study was conducted at the Pediatric Nephrology Unit at Zagazig University Hospitals over a period of six months. The study included 40 nephrotic children in different disease activity and 40 healthy controls matched for age and sex. All participants underwent complete history-taking, physical examination, and laboratory studies, including fibrinogen, protein C, protein S (By ELISA) AT III and platelet indices. Results: Plasm levels of protein S, protein C and AT III during activity (onset and relapse) were significantly lower than their levels at remission and in healthy controls. The mean level of fibrinogen was significantly higher during activity than its level during the remission period and in the control group. Correlations between changes in coagulation parameters and biochemical findings were also investigated. Serum albumin levels were positively correlated with plasma AT III, PC, and PS (P <0.001). Mean platelet number was significantly higher during activity (onset and relapse) than in the remission period and in the control group. Conclusion: This study reveals that the hemostatic abnormalities in nephrotic children involve mostly high fibrinogen and platelet count. But low protein S, protein C, ant thrombin III, and mean platelet volume. Variations of values may be related to disease state.
Keywords: Nephrotic Syndrome, Hemostasis, Thromboembolism, Children

INTRODUCTION

Nephrotic syndrome is distinguished by a disturbance in the permeability of the glomerular capillary wall at the bowman capsule, which makes it incapable of limiting the loss of proteins through the urine[1].

In nephrotic syndrome, proteinuria and hypoalbuminemia are the main risk factors for thromboembolic episodes [2].

Thrombotic events of the venous or arterial circulation might exacerbate the hypercoagulable state known as nephrotic syndrome (NS) [3].

Increased glomerular capillary wall permeability in nephrotic syndrome causes significant protein losses in urine, which in turn causes hypoalbuminemia. Affected children's urine also contains reduced levels of anticoagulant components, such as antithrombin, protein C, and protein S, in addition to albumin [4].

As a result, the vascular system is more susceptible to blood hypercoagulability and plasma anticoagulant factor levels are lower [5].

Increased platelet count, aberrant platelet function, hypovolemia, Due to increased hepatic synthesis of pro-coagulants like Factors I, V, and VIII, children

with nephrotic syndrome are also susceptible to aberrant coagulation. When these conditions come together, the child with nephrotic syndrome is more likely to experience hypercoagulation, which can lead to thromboembolic episodes [4].

The risk of getting thromboembolism (TE) in children with nephrotic syndrome ranges from 1.8% to 5%. It is challenging to ascertain the actual prevalence of thromboembolic consequences in children with NS since many of them are asymptomatic and subclinical, despite the fact that the majority have been reported in membranous nephropathy in adulthood [6].

Given the comparatively high prevalence of TE in NS and its potentially dangerous character, determining the risk factors that contribute to TE is essential [7].

AIM OF THE WORK

The study aimed to evaluate the coagulation profile and platelet indices in nephrotic children during active and remission periods and to compare the results with those from the healthy controls. The evaluation of these coagulation abnormalities may act as a valuable resource for physicians, facilitating timely and suitable interventions, thereby enhancing the overall care of children affected by this condition.

METHODS

This case- control study was conducted at the Pediatric Nephrology Unit, Zagazig University Hospitals. The study was conducted from March 2024 to September 2024. 40 nephrotic children and an equal number of seemingly healthy controls who fit the inclusion criteria in terms of age and gender were included in the study. Participants in the study ranged in age from 1 to 15 years. The nephrotic group was further divided into two subgroups: (the active group included 7 new cases and 18 relapse cases, and the remission group included 15 cases). There were 29 males and 11 females.

Diagnosis of NS established by edema, serum albumin levels below 2.5 g/L, urine protein-creatinine ratios more than 2 mg/mg, severe proteinuria with 3+ or 4+ protein on a dipstick urinalysis, and hypercholesterolemia (cholesterol levels more than 350 mg/dL) [8]. Relapsed NS is defined by a urinary protein–creatinine ratio (uPCR) of 200 mg/mmol or greater, or a urine dipstick test showing more than 3+ protein, sustained for three consecutive days [9]. Complete remission is characterized by a uPCR of less than 20 mg/mmol or a urine dipstick test less than 1+, maintained for three consecutive days [9].

The inclusion criteria were children diagnosed with nephrotic syndrome (new cases, relapse, or remission cases), aged between 1-15 years old for the nephrotic group, and healthy children without chronic or acute conditions for the control group. Exclusion criteria were refusal to participate in the study, children with hypercoagulable states due to causes other than nephrotic syndrome, patients with chronic illnesses like sickle cell anemia, and patients receiving drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) or oral anticoagulants like heparin.

All participants were subjected to complete history-taking (personal history, drug history, relapse frequency, and duration of disease). Physical examination, including general and local examination, was done for all study populations.

laboratory investigations for all participants included: Complete blood count (CBC) using Sysmex XN 330 (Sysmex, Japan), liver function tests (total protein, serum albumin, bilirubin, AST, ALT), blood urea nitrogen (BUN)and creatinine), Lipid profile (cholesterol, triglyceride), 24 hr. urine collections for Protein-creatinine ratio (PCR) using fully automated Cobas 8000-C702 (Roche, Germany), and coagulation profile using fully automated CA 1500 (Sysmex, japan)

Coagulation tests:

Fibrinogen by fully automated Sysmex CA 1500.

Combine one part (3.2 %) of solution of sodium citrate with nine parts of recently drawn patient blood. The blood sample should be centrifuged at 1,500 × g for at least 15 minutes at room temperature. Keep at room temperature in an unopened tube. Because cold activation of FVII may change results, samples were not stored on ice or between 2 and 8 °C. Within 24 hours after blood collection, plasma was analyzed. The samples were kept for a maximum of five minutes at 37°C.

Anti thrombin III: by fully automated Sysmex CA 1500

The INNOVANCE® In the antithrombin assay, a chromogenic measurement principle is employed. Factor Xa is added in excess to citrated plasma. When heparin is present, the antithrombin in the sample complexes with part of the enzyme and renders it inactive. A dye is then released when excess, unrestrained factor Xa cleaves a certain chromogenic substrate. The rise in the absorbance value at 405 nm indicates the rate of substrate cleavage.

Protein C (PROC) and Protein S (PROS):

PROC and PROS in human plasma were measured in vitro using a sandwich enzyme immunoassay (ELISA) kit.

Ethics considerations:The institutional review board (IRB#11288-8-11-2023), Faculty of

Medicine, Zagazig University, approved the whole study design. Approval from the hospitals and families of the children. The Declaration of Helsinki, the International Medical Association's code of ethics for research involving human subjects, was followed in the conduct of this study.

Statistical analysis:

SPSS (Statistical Package for the Social Sciences) version 26 was used to gather, tabulate, and statistically analyze all of the data. The chi-square test was used to compare quantitative data between two groups, the independent samples, and characterize categorical variables according to their absolute frequencies. For regularly distributed data, the t-test was utilized, and for non-normally distributed data, the Mann-Whitney test was utilized. When significant differences were found, pairwise comparisons were carried out using Bonferroni correction. One-way ANOVA, the ROC curve test, the independent sample T test, the Kruskal-Wallis test, and the Mann-Whitney test were also employed in this study. The change in one variable over two time points within the same group was examined using the appropriate statistical methods. The ROC curve was used to determine the optimal cutoff of a specific quantitative measure when diagnosing a particular health problem. Linear regression analysis was utilized to measure associated independent components for the dependent factor. P <0.05 was chosen as the threshold for statistical significance. There was a highly significant difference if p ≤0.001.

RESULTS

The study group consisted of 40 nephrotic cases and 40 healthy controls, with male predominance (72.5% in the case group, and 60% in the control group). Out of 40 nephrotic patients in this study, 25 were in activity (7 new cases and 18 were in relapse) who were hospitalized and treated with prednisolone. The remaining 15 were fulfilling the criteria of remission. The groups under investigation did not differ statistically in terms of age, sex, height, weight, or body mass index (table 1). The platelet indices of the nephrotic and healthy groups showed statistically significant variations, the nephrotic children's MPV was lower than the control groups. On the other hand, patients had a greater platelet count than controls. (table1). Similarly, mean platelet count in active nephrotic was 466.64± 126.33 and in the remission group it was 335.53±99.59(P<0.001), MPV mean values were 8.63 ± 0.86 and 9.23 ± 1.07 in the active and remission groups, respectively, P <0.001) (table 3).

Total cholesterol and triglycerides were significantly higher among nephrotic groups and subgroups versus control groups, P <0.001 (tables 1, 3).

Hemostatic factors differed significantly among studied groups as shown in (table 2, 3, and figure 2).

Protein S, protein C, and AT III mean levels throughout the activity period were considerably lower (P <0.001) than those during the remission phase and control group. Compared to the control group and the remission phase, the mean fibrinogen level during the activity period was noticeably higher (4.94 ± 1.08, 3.15 ± 0.82, 2.78 ± 0.45, P <0.001).

Compared to the remission and control groups, the active group's mean platelet count was noticeably greater. On the other hand, the active and the remission group`s mean platelet volume was significantly lower than the control group. Ant thrombin III and protein S and C mean levels during the relapse period were substantially lower than those in the control group and during the remission phase. (table 3).

The best cutoff of protein S in the diagnosis of nephrotic syndrome is ≤ 82.95% with an area under the curve 0.85 (95% CI; 0.757 to 0.943) with sensitivity 87.5% and specificity 75% (p <0.001) (figure 1). (Table 4).

Table 1: Comparison between the studied groups regarding demographic and laboratory data:

	Case group N=40 (%)	**Control group N=40 (%)**	**χ^2**	**P**
Sex Female Male	 11 (27.5%) 29 (72.5%)	 16 (40%) 24 (60%)	1.389	0.237
	Mean ± SD	**Mean ± SD**	**t**	**P**
Height (cm)	124.14 ± 20.25	131.43 ± 18.48	-1.682	0.097
BMI (kg/m^2)	18.02 ± 4.82	18.54 ± 2.18	-0.623	0.535
Hemoglobin (g/dl)	12.62 ± 2.03	12.38 ± 1.62	0.584	0.561
Platelet (×10µL)	417.48±132.34	261.95 ± 83.14	6.924	<0.001**

	Case group N=40 (%)	Control group N=40 (%)	χ^2	P
MPV (fl)	8.85 ± 0.98	9.79 ± 0.91	-4.429	<0.001**
Albumin (g/dl)	1.86 ± 0.48	3.93 ± 0.4	-21.056	<0.001**
Cholesterol (mg/dl)	406.24 ± 90.85	194.58 ± 30.56	13.967	<0.001**
	Median (IQR)	Median (IQR)	Z	P
Age (year)	7.5(2-14)	8(4-14)	-1.115	0.266
Weight (kg)	26.63(21.11 – 32.15)	29.7(23.78 – 39.08)	-1.925	0.054
Urea (mg/dl)	17.1(15 – 20)	13.05 (10.83 – 17)	-3.306	<0.001**
Creatinine (mg/dl)	0.73(0.6 – 0.9)	0.31 (0.23 – 0.41)	-7.262	<0.001**
Triglycerides (mg/dl)	292.5 (252.5 – 379)	118 (100 – 122)	-7.559	<0.001**

χ^2Chi square test t independent sample t test Z Mann Whitney test
*p<0.05 is statistically significant **p≤0.001 is statistically significant highly significant

Table 2: Comparison between the studied groups regarding coagulation profile:

	Case group Mean ± SD	Control group Mean ± SD	T	P
Protein S (ng/ml)	78.41 ± 4.22	100.37 ± 20.02	-6.789	<0.001**
Protein C (ng/ml)	83.69 ± 9.83	104.85 ± 16.38	-7.007	<0.001**
Antithrombin III (%)	86.67 ± 18.32	104.24 ± 17.94	-4.334	<0.001**
Fibrinogen (g/dl)	4.27 ± 1.31	2.78 ± 0.45	6.813	<0.001**

t independent sample t test **p≤0.001 is statistically significant highly significant

Table3: Platelet indices, lipid profile and coagulation in various diseases state

	Active group N=25	Remission group N=15	Control group N=40	χ^2	P
Onset	New 7 Relapse18				
	Mean ± SD	Mean ± SD	Mean ± SD	F	P
Platelet (×10µL)	466.64±126.33	335.53±99.59	261.95±83.14	20.565	<0.001**
Bonferroni	P_1 <0.001**	P_2 0.057	P_3 <0.001**		
MPV (fl)	8.63 ± 0.86	9.23 ± 1.07	9.79 ± 0.91	31.374	<0.001**
Bonferroni	P_1 0.153	P_2 0.149	P_3 <0.001**		
lipid profile					
Cholesterol (mg/dl)	444.36 ± 90.01	342.71 ± 46.75	194.58 ± 30.56	146.217	<0.001**
Bonferroni	P_1 <0.001**	P_2 <0.001**	P_3 <0.001**		
	Median (IQR)	Median (IQR)	Median (IQR)	KW	P
Triglycerides (mg/dl)	320(288 – 435)	250(185 – 270)	118(100 – 122)	62.066	<0.001**
Pairwise	P_1 0.026*	P_2 <0.001**	P_3 <0.001**		
Coagulation profile	Mean ± SD	Mean ± SD	Mean ± SD	t	P
Fibrinogen (g/dl)	4.94 ± 1.08	3.15 ± 0.82	2.78 ± 0.45	63.576	<0.001**
Bonferroni	P_1 <0.001**	P_2 0.321	P_3 <0.001**		
Protein S (ng/ml)	77.17 ± 2.04	80.47 ± 5.94	100.37 ± 20.02	23.136	<0.001**
Bonferroni	P_1 >0.999	P_2 <0.001**	P_3 <0.001**		
Protein C (ng/ml)	80.2 ± 8.15	89.5 ± 9.87	104.85±16.38	28.02	<0.001**
Bonferroni	P_1 0.103	P_2 <0.001**	P_3 <0.001**		
Antithrombin III (%)	77.48 ± 5.3	101.97 ± 22.04	104.24±17.94	22.671	<0.001**
Bonferroni	P_1 <0.001**	P_2 >0.999	P_3 <0.001**		

t independent sample t test F One way ANOVA test KW Kruskal Wallis test *p<0.05 is statistically significant **p≤0.001 is statistically significant highly significant p1 difference between active NS and remission group p2 difference between remission and control group p3 difference between active NS and control group

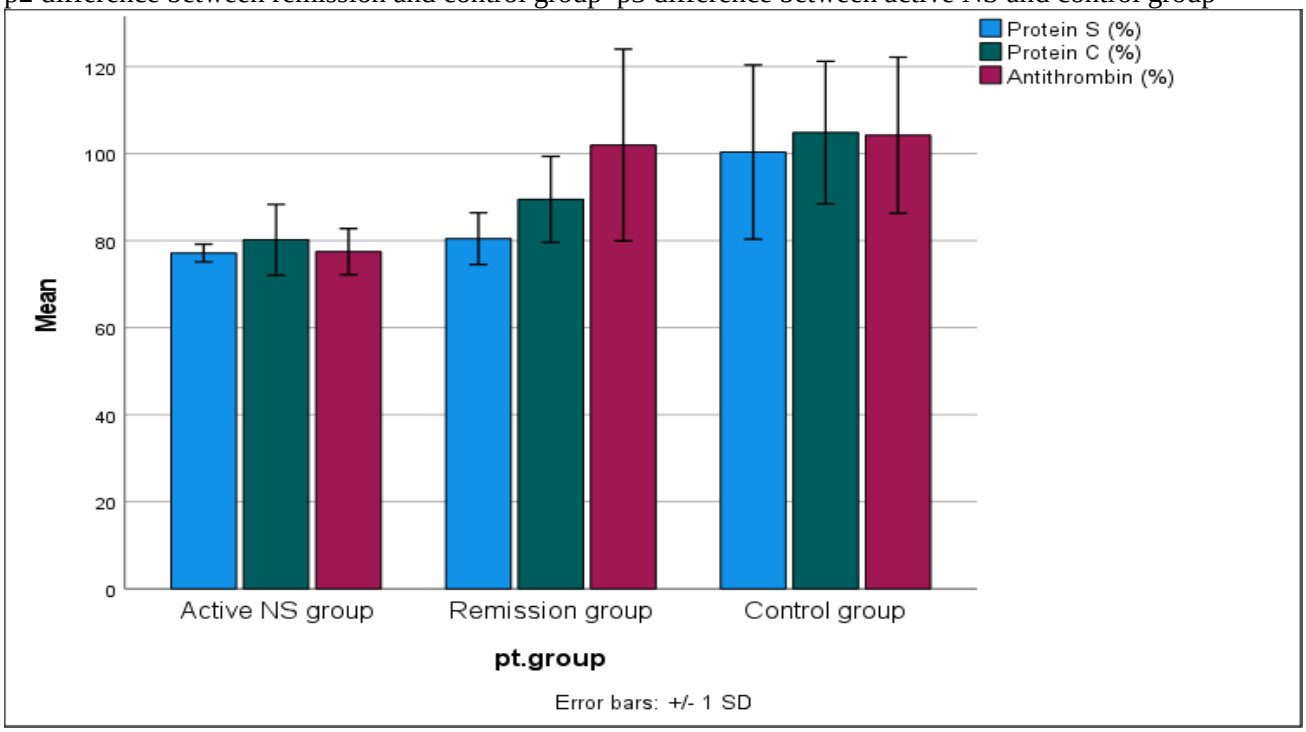

Figure 1: Simple bar chart showing comparison between groups regarding protein C, S and ant thrombin.

DISCUSSION

Thromboembolic episodes are more frequent in nephrotic syndrome. Hypovolemia, hypercoagulability, and infections all raise the risk of thrombosis. The risk of thrombosis is also raised by thrombocytosis, reduced coagulation inhibitors, and elevated procoagulants.

The study participants in the nephrotic group were 7.98 ± 3.34 years old on average. There was a 72.5% male preponderance in the study. Age, sex, height, weight, and BMI did not significantly differ between the patient and control groups.

In the active period, the mean platelet count was statistically significantly higher than in the remission and control groups ($p < 0.001$) (table 1.3). In contrast, the mean MPV was substantially lower in the active phase than in the remission phase and in the control group. Gamal et al. [10] have reported similar findings. Ismail et al. [12] and Kaan Gulleroglu et al. [11] also produced findings that concurred with ours. In patients with nephrotic syndrome, a study by Wasilewska et al. [13] showed that the mean platelet count and mean platelet volume were negatively correlated.

The precise mechanism underlying elevated platelet counts in nephrotic syndrome remains unclear. Nonetheless, it has been noted that hypoalbuminemia and hypercholesterolemia are associated with increased platelet numbers and hyper aggregation [14, 15].

It is well recognized that platelets are essential to the pathophysiology of thrombotic alterations in NS. It is thought that biochemical abnormalities linked to hypoalbuminemia cause greater platelet aggregation, which in turn causes raised platelet counts in nephrotic syndrome, albeit the precise mechanism underlying this phenomenon is unknown. Platelet counts are adversely correlated with hypoalbuminemia since they should revert to normal when the patient enters remission [4].

In our investigation, patients' mean platelet volume (MPV) was considerably lower than controls' (8.85 ± 0.98) (9.79 ± 0.91), $p < 0.001$.

During nephrotic syndrome activity, Wasilewska et al. [13] reported reduced MPV and greater platelet counts. This improved following corticosteroid therapy, with serum albumin normalizing earlier than platelet and MPV values.

An imbalance between thrombotic and antithrombotic factors causes the hypercoagulability state associated with nephrotic syndrome. Due to compensatory protein production in the liver, high molecular weight proteins like fibrinogen are elevated, whereas some low molecular weight proteins are eliminated in the urine. Numerous investigations have revealed that NS has an elevated amount of fibrinogen.

The active group's mean fibrinogen level was substantially higher in our study (4.94 ± 1.08) than

in remission (3.15 ± 0.82) and in the control group (2.78 ± 0.45) p <0.001.

According to research by Such-Gruchot et al. [16], children with active disease (onset or relapse) had higher fibrinogen levels. This conclusion is consistent with our findings.

Tarigan et al. [17] who sought to assess children with nephrotic syndrome's hemostatic factors. Similar to our study, they found that the mean fibrinogen level during relapse was considerably greater than that during the remission phase and in the control group.

Enhanced hepatic production in reaction to albumin depletion in NS causes hyperfibrinogenemia, which has been linked to an increased vulnerability to thromboembolism and hypercoagulability [18].

In our study, the levels of natural anticoagulants were significantly reduced in patients compared to controls. Protein S levels were notably lower in patients (78.41 ± 4.22) than in controls (100.37 ± 20.02), p <0.001. Similarly, protein C levels were decreased in patients (83.69 ± 9.83) compared to controls (104.85 ± 16.38), p <0.001. Antithrombin III activity percentages also showed a significant reduction in patients (86.67 ± 18.32%) versus controls (104.24 ± 17.94%), p <0.001.

Mittal et al. [19] discovered that NS patients with start and relapse had low AT levels; nevertheless, these values fell within the lower bound of normal and did not substantially differ from those of children in remission. Antithrombin and albumin losses in the urine were thought to be the cause of this decrease in AT levels.

Odimegwu et al. [4] revealed that nephrotic and non-nephrotic children had median AT values that were within the reference range, at 142% and 131%, respectively. When comparing the AT levels of nephrotic children to those of seemingly healthy controls, no discernible difference was seen. Furthermore, when taken into account in different disease states, all of the median AT levels fell within the normal range and did not deviate significantly from either the disease states or the controls. The result of this study revealed that the AT levels of nephrotic children were normal, suggesting that there is no change in the quantitative levels of AT in these children.

This is further supported by Kerlin et al. [20], who found that proteinuria in nephrotic syndrome dramatically decreased AT activity rather than plasma AT levels. Investigators deduced that the deficiency of antithrombin in the context of active nephrotic syndrome may have resulted from a qualitative impairment in enzymatic functionality rather than a reduction in the quantitative levels.

In our study, the levels of protein S were significantly reduced in patients compared to controls. were notably lower in patients (78.41 ± 4.22%) than in controls (100.37 ± 20.02%), p <0.001, also lower among children with active disease as opposed to those in remission (Protein S at 77.17 ± 2.04% versus 80.47 ± 5.94%). This finding is similar to Mortazavi et al. [7] who showed low protein S levels in nephrotic compared to the control group.

Also agree with Wygledowsk et al. [21] , who showed significantly lower protein S levels at the active NS in comparison to the control group and elevated at the remission period.

In our study, patients with active NS had considerably lower amounts of protein C than the control group.

This finding aligns with Meena et al. [22] and Niaudet, [23], who reported reduced protein C levels in NS: this may be explained by loss of protein C in the urine of nephrotic patients, especially with severe proteinuria.

However, reports on variations in the amounts and characteristics of protein C are contradictory. El Ghannam et al. [24] showed that there was an increase in level of P-C in NS, explained by increased synthesis of protein C by the liver secondary to proteinuria. TE may be prevented by an increase in protein C activity, according to Ozkayin et al. [25].

In contrast to controls, our investigation showed that individuals with nephrotic syndrome had severe dyslipidemia. Total cholesterol levels were markedly elevated in patients (406.24 ± 90.85 mg/dl) versus controls (194.58 ± 30.56 mg/dl, p <0.001). Additionally, patients' triglyceride levels were noticeably increased, and heavy proteinuria as, onset, relapse associated with more dyslipidemia and increased risk of thromboembolism.

Tao et al. [26] discovered that the majority of patients with clinical NS also exhibit aberrant lipid metabolism, which is consistent with our findings. Dyslipidemia among NS patients is a recognized risk factor for heart infarction and cardiovascular mortality.

Also, Hari et al. [27] found that children with chronic NS exhibit significant dyslipidemia, which probably significantly raises their chance of developing cardiovascular problems in the future. There is a direct correlation between the severity of proteinuria and the degree of dyslipidemia in NS.

In addition, Yanai [28] revealed that nephrotic syndrome is one of the main causes of subsequent hyperlipidemia.

In our study, the analysis of protein parameters revealed significantly lower total

protein and albumin levels in patients compared to controls. Furthermore, albumin levels showed strong positive correlations with natural anticoagulants, emphasizing the relationship between protein levels and anticoagulant status in the study population.

Gashaw et al. [29] demonstrated that a low serum albumin level was a significant predictor of relapse in children with nephrotic syndrome. Children with serum albumin levels below 1.5 g/dl showed a 4.34-fold increased risk of relapse compared to those with levels above 1.5 g/dl, even after adjusting for the impact of other variables.

Regarding serum urea and creatinine, our study found significant distinctions in their levels between the groups under investigation (significantly increased in the patients group).

In accordance, Zaorska et al. [30] found that the level of s-creatinine was noticeably greater in nephrotic syndrome patients than in the healthy controls.

This disagrees with El hamshary et al. [31] They found no statistically significant difference between the control group and the patient group (children with idiopathic nephrotic syndrome) in terms of serum creatinine and blood urea.

Our research determined a threshold of ≤82.95 ng/ml for Protein S, with an area under the curve of 0.85 (95% CI 0.757 to 0.043), 87.5% sensitivity, and 75% specificity.

Conclusion:

In conclusion, we discovered a few biological abnormalities in the research subjects, such as thrombocytosis, low MPV, higher amounts of fibrinogen, and lower levels of protein C, S, and AT III in patients with nephrotic syndrome. Patients with severe proteinuria should be regularly monitored for thromboembolism since these abnormalities raise the risk of thrombosis.

Limitation:

There was a tiny sample size. To generalize the findings, the study must be conducted in a multicenter with a larger sample. Because of its cross-sectional nature, the study did not permit subject follow-up. In all disease states, sample sizes were somewhat modest. Due to financial limitations, the number of assays on procoagulant factors was restricted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FINANCIAL DISCLOSURES

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