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Assessment of disease progression in children with nephrotic syndrome using atherogenic indicators

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Background
The nephrotic syndrome (NS) raises the risk of atherosclerosis and endothelial dysfunction. Endothelial dysfunction was measured and linked with dyslipidemia and inflammatory markers in individuals with nephrotic syndrome. LDL-cholesterol, total cholesterol, and fibrinogen are the most critical variables implicated in endothelial dysfunction in the nephrotic syndrome.
Objective
The study's goal was to evaluate atherogenic indicators as markers that can be utilized to determine both atherogenic potential and cardio metabolic health.
Materials and methods
This study was designed as a case-control study, A total of 52 participants age range (9-12) year with nephrotic syndrome.
Sample collection
Collected from Kerbala pediatric teaching hospital, Iraq. Serum lipid panel (Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL) and triglycerides (TG), renal function test (blood urea and creatinine) albumin in serum and urine were all measured for the study groups.
Results and conclusion
The results of the study showed a massive increasing in the mean levels of the atherogenic indices in (NS) patients compared to the control group. Diagnostic thresholds point of the atherogenic indices were indicated that most of the measured indices shown a highly sensitivity and specificity toward the lipid complication in (NS) case. In our point of view, theses indices provided novel clues on the atherogenic mechanisms in such cases, which might reflect the inflammatory signals more effectively than lipid panel.

Keywords: atherogenic indices, dyslipidemia, nephrotic syndrome

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Introduction

The term 'nephrotic syndrome' (NS) refers to a clinical disease that is distinguished by substantial amounts of protein being excreted in the urine. Hypoalbuminemia, which leads to hyperlipidemia, edema, and a host of other health problems, is caused by proteinuria. It is possible to pinpoint the root cause of this issue, which is an increase in permeability brought on by the renal glomerulus's damaged basement membrane. The most frequent causes of this syndrome are infections and thromboembolic illnesses. It is caused by an abnormality in the glomerular permeability, which may be secondary by congenital infections, diabetes, systemic lupus erythematosus, neoplasia, or the use of particular drugs, or it may be the primary outcome of an intrinsic renal disease in the kidneys. It results from an anomaly in the glomerular permeability in any scenario [1].

Atherogenic indices

Dyslipidemia is thought to be a significant risk factor for coronary artery disorders (CAD) [2]. A number of lipid indicators have already been used to forecast the likelihood of developing coronary atherosclerosis and cardiovascular diseases (CVD). Plasma lipid and lipoprotein concentrations make for the majority of these, with sporadic involvement from plasma apo lipoproteins. The new use of lipid ratios as risk markers for lipids and lipoproteins is fascinating [3]. Numerous studies show the value of modifying lipid ratios over traditional lipid markers [4]. These indices were calculated by the following equations:

Atherogenic coefficient (AC): AC=non-HDL-C / HDL-C ; Non- HDL-C=TC–HDL-C

Atherogenic index of plasma (AIP): AIP=log (TG/ HDL-C)

Castelli's risk indexes (I and II): CRI-I=TC/ HDL-C ratio; CRI-II=LDL-/ HDL-C ratio.

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Cholesterol index: (C. index= (LDL-C)–(HDL-C)

The hyperlipidemia condition of nephrotic puts them at an elevated risk for cardiovascular disease depending on the lipid anomalies' type, and the risk varies [5]. There have been no documented instances of the particular nephrotic syndrome in Karbala. However, the incidence rate of new cases has been recorded at Al-Kadhimiya Teaching Hospital in Baghdad. During the course of the study, a cohort of 4785 children were included, among 326 cases of renal diseases were identified, namely nephrotic syndrome (n=52; 15.9%) [6]. The goal of this study is to evaluate the possible contribution of these indices to atherogenicity among nephrotic syndrome cases, which is based on the research premise that children with nephrotic syndrome may be at high risk of accelerated atherogenesis.

Materials and methods

The study design

A total number of 100 samples were collected from (52) cases of nephrotic syndrome after a fully diagnosis by a specialist pediatric nephrologist and consultant and 48 participants as a healthy control. The protocol for the research received clearance from the ethical committee, all participants or their relatives gave written informed consent. Assessment of nephrotic syndrome was performed by specialist nephrologist consultant.

Blood collection

Blood sampling, five ml of venous blood was withdrawn, allowed to clot for 1 h, centrifuged at 3000 rpm, then serum was separated after 15 min of the centrifugation, and finally stored at −80°C until biochemical assessment of Serum lipid panel which was performed using Roche diagnostics /cobas c111 Auto analyzer/ Chemistry System /Germany, the cobas c111 main instrument uses absorption photometry for determining the amount of absorbance in a fluid.

Ethical considerations

Written illustrative consent form was signed by all parents/caregivers of the participating patients. This study was performed according to the ethical rules for medical research involving human participants of the Declaration of Helsinki (1964). Ethical approval was received from the ethical and research committee of Department of Biochemistry, College of Medicine, University of Kerbala, Iraq

Statistical analysis

The distribution of the data was examined using the Shapiro-Wilk test, a numerical technique for assessing normality. The association between the research's parameters was evaluated using odds ratios (ORs) and a 95% Confidence Interval Range generated using a non-conditional logistic regression. Analytical statistical studies confirmed that there were notable differences in the categorical variables between the parameters. The results were deemed statistically significant if the two-sided P value for each hypothesis test was $\leq$0.05. ROC analysis is the study of receiver operating characteristics. A P value of $\geq$0.05 was deemed as statistically significant, and all P values were found to be two-sided.

Results

A total number of 100 samples were collected from 52 cases of nephrotic syndrome after a fully diagnosis by a specialist pediatric nephrologist and consultant and 48 participants as a healthy control. Table 1 lists the research groups' clinical demographics, laboratory results, and other relevant information. Out of n=52 cases, (63.5%) were males and (36.5%) were females. The mean age of the cases was 7.67 years. The range age of participants was within (1–12) years old, (11%) of the patient was within (1–4) years, while (17%) of the patient were within age range (5–8), and (24%) of the patients were in age range (9–12) years. Also, the analysis of data illustrated that (38.46%) of the patients were having duration of disease (4–8 Years), while (34.62%) were having duration within (<one Year), and 26.92% of the patients group were having duration (1-3 Years).

Table 1 The demographic characteristics of the study population (N=100) were described

Variable	Groups	Patient N=52	Control N=48
Age groups	1–4 Years	11	14
	5–8 Years	17	20
	9–12 Years	24	14
Sex	Male	33	25
	Female	19	23
Duration of disease	0	0	48
	< one Years	18	0
	1–3 Years	14	0
	4–8 Years	20	0

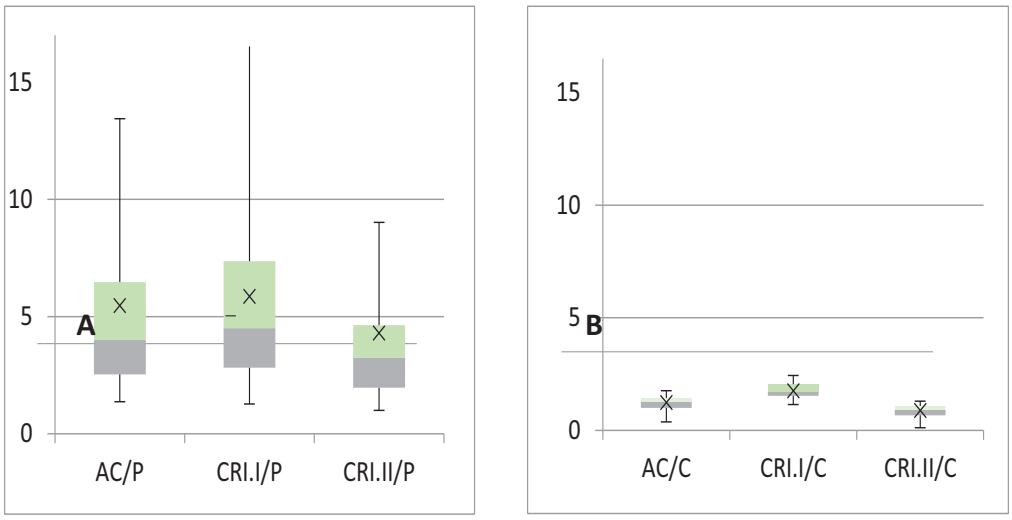
The examination of the level of atherogenic indices in the nephrotic syndrome group compared to the control

The risk of dyslipidemia complication among children with nephrotic syndrome needs to be considered, this study was focus on the calculation of atherogenic indices in the patient group and compared it to healthy control. Results indicated that there were massive increases and significant differences in the mean level of the atherogenic coefficient (AC), atherogenic index of plasma (AIP), Castelli's risk indexes (I and II), and cholesterol index (C. index) that measured in the patient group when compared to healthy control Figs. 1 and 2.

The relationship between the degree of atherogenic indices in nephrotic syndrome and disease duration

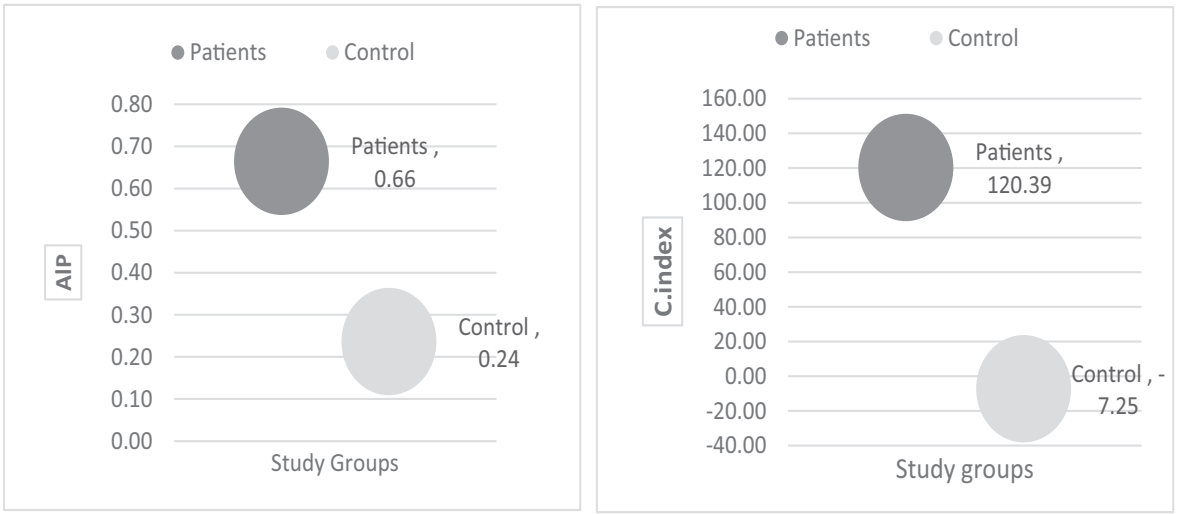
This study was examined the atherogenic indices based on the duration of nephrotic syndrome. Generally, patients with nephrotic syndrome were shown a marked difference in the mean level of (AC, AIP, CRI.I, CRI.II and C. index) when comparing the duration of disease. Due to their hyperlipidemia condition, nephrotic are more susceptible to cardiovascular disease. The kind of lipid abnormalities affects the risk differently [5].

Figure 1



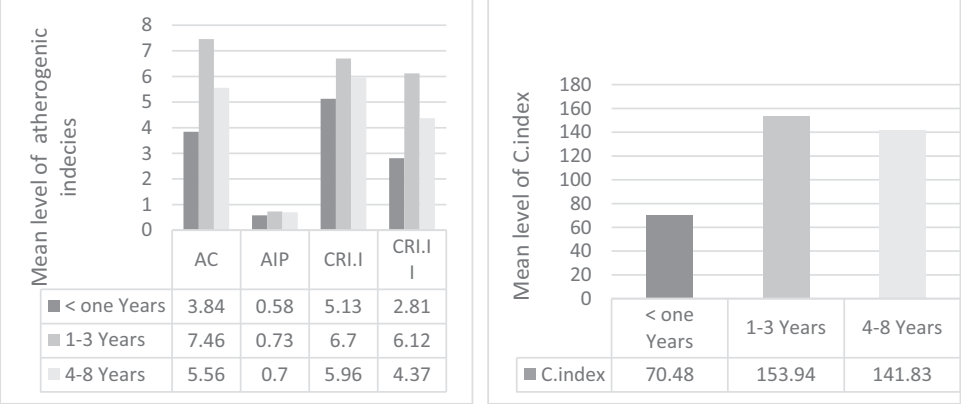
The distribution of blood levels of atherogenic coefficient (AC) and Castelli's risk indicators (I and II) in the nephrotic syndrome group: (**A**) Compared to the control group. (**B**) Depicted in a boxplot.

Figure 2



Mean differences in blood levels of atherogenic index of plasma (AIP) and cholesterol index (C. index) between the nephrotic syndrome and control groups.

Figure 3



Difference in mean levels of atherogenic index in nephrotic syndrome with duration Group 1 (one year), Group 2 (one to three years), and Group 3 (4 to eight years).

Table 2 Shows the effect of sex on biochemical indicators in the patients and control groups

	Male			Female		
Biomarker	Patients *N*=33	Control *N*=25	*P* value	Patients *N*=19	Control *N*=23	*P* value
AC	5.41±4.66	1.26±0.31	<0.001	5.58±4.30	1.21±0.35	<0.001
AIP	0.66±0.33	0.24±0.09	<0.001	0.67±0.27	0.23±0.08	<0.001
CRI.I	6.06±4.65	1.78±0.36	<0.001	5.54±3.38	1.73±0.33	<0.001
CRI.II	4.20±3.97	0.91±0.26	<0.001	4.47±3.84	0.86±0.32	<0.001
C. index	109.33±102.0	−5.83±14.69	<0.001	139.6±112.	−8.78±19.71	<0.001

Results of atherogenic indices of nephrotic syndrome showed a fluctuating outcome, which is likely due to the fact that in the majority of patients, renal failure or other systemic disorders are present in addition to the nephrotic syndrome, or because the patients are undergoing treatment with corticosteroids, which has confounding effects on the lipoprotein patterns [7]. Results was indicated that C. index were increased significantly when compared patient's groups who have duration of less than one year with a group who have duration 1-3 years, *P* value less than 0.05 as presented in Fig. 3.

The difference in biochemistry, lipid profile, and atherogenic index levels between sex groups in nephrotic syndrome

Table 3 illustrated the mean level of the biochemical in the patients and control groups according to the sex. On the other hand, a very few studies have investigated the association between atherogenic indices and nephrotic syndrome or at least revealed the potential clinical usefulness [8]. Therefore, our study was also focus on the estimation of atherogenic coefficient (AC), atherogenic index of plasma (AIP), Castelli's risk indexes (I and II), and cholesterol index (C. index) and investigated their differences based on sex groups. Results were shown a massive increased in the mean levels of atherogenic indices in both sexes compared to health control group as presented in Table 2.

The difference in atherogenic index levels in nephrotic syndrome based on age groups

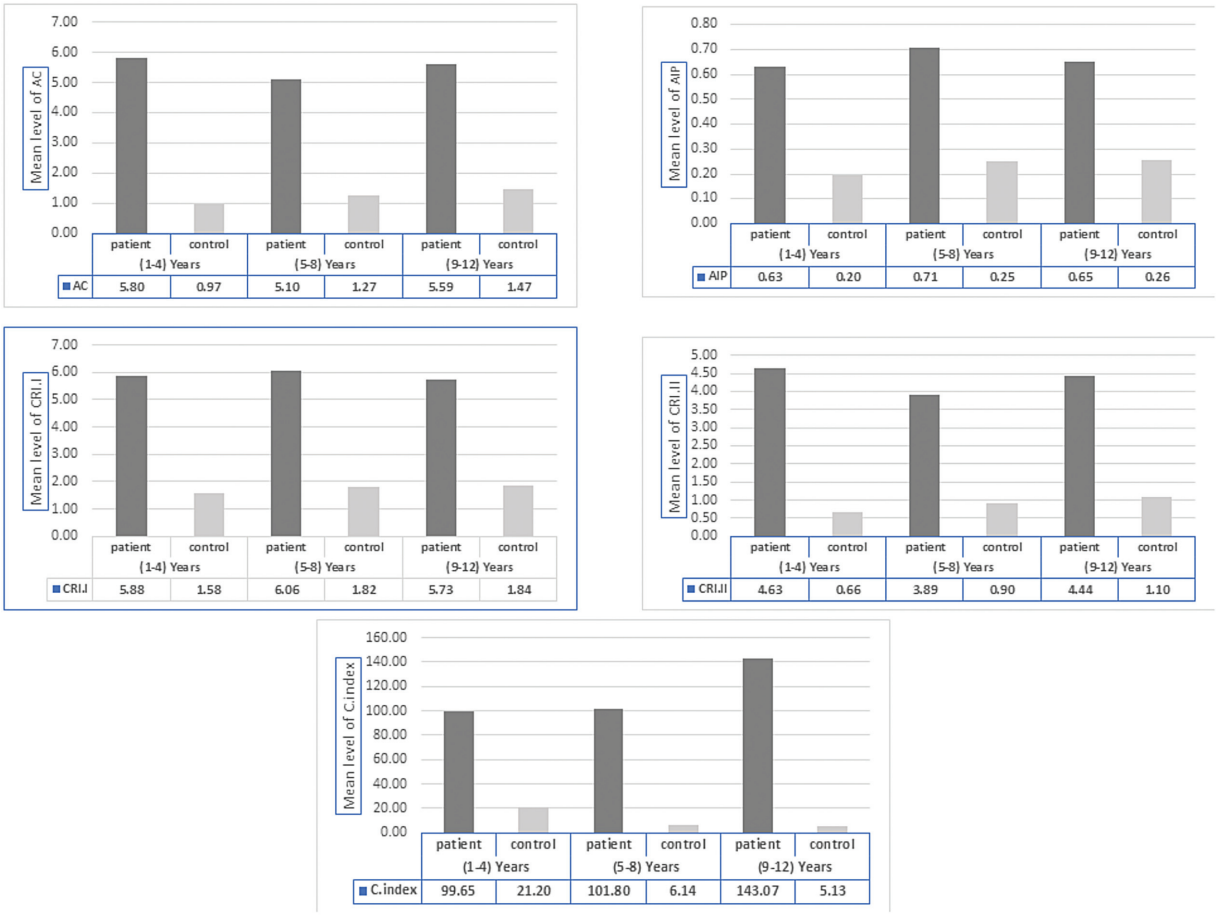
In Fig. 4 a comparison of serum level of (AC, AIP, CRI.I and II, C. index) in different age groups was performed. The level of indices increasing in case compered to control within the age groups ((1–4),

Table 3 Shows the estimated associations of the studied factors (AC, AIP, CRI.I, CRI.II, and C. index) in nephrotic syndrome patients in comparison to the control group

Biomarkers	OR	*P* value
AC	115.65	<0.001**
AIP	62.817	<0.001**
CRI.I	1.22	0.271*
CRI.II	89.041	<0.001**
C. index	110.266	<0.001**

*= Non significant. **= Significant. CI, Confidence Interval; OR, Odds Ratio.

Figure 4



Mean differences in atherogenic indices measured in children with nephrotic syndrome against healthy controls based on age group.

(5–8) and (9–12)) years. A highly statistically significant differences were found in all age groups.

Investigate the relationship between biomarkers and patient groupings

Binary logistic regression was performed to analyze the associating of the (AC, AIP, CRI.I, CRI.II and C. index) with the nephrotic syndrome. It was found that the biomarkers (AC, AIP, CRI.II and C. index) shown a highly significant differences in patient and represented as a risk factor (OR: 115.65, OR: 62.817, OR: 89.041 and OR: 110.266) respectively, as shown in Table 3.

Receiver operating characteristic analysis

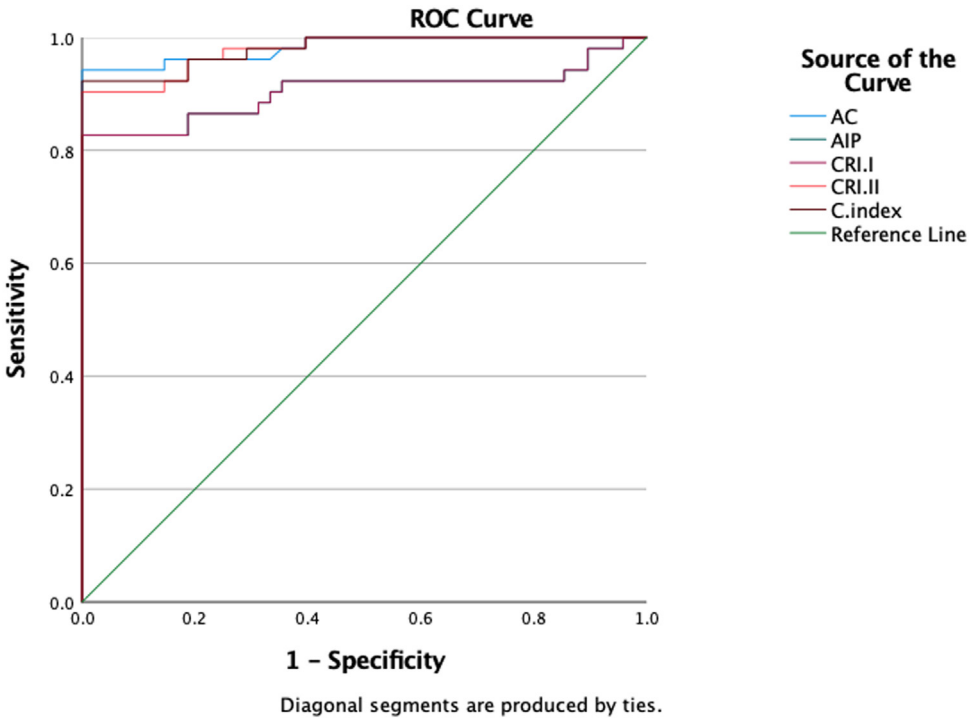
The results of receiver operating curve (ROC) analysis were used to determine the best diagnostic points for identifying dyslipidemia complications in instances with nephrotic syndrome. In Table 4, the diagnostic cutoffs for the atherogenic indices were reported. The findings showed that majority of the measured indices had excellent sensitivity and specificity for the (NS) condition, with *P* values of 0.001. To the best of our knowledge, this is a thorough investigation on the best diagnostic indicators for identifying complications related to nephrotic syndrome. The *P* values were extremely statistically significant at 0.001. Youden's J

Table 4 Receiver operating characteristic curve demonstrating the sensitivity and specificity of atherogenic indices in patients versus controls

Variable	AUC	Specificity %	Sensitivity %	*P* value	Cut-off points	Youden index	CI (95%)
AC	98.3%	98%	94.20%	<0.001**	1.7976	0.942	(0.962–1.000)
AIP	90.4%	97%	82.70%	<0.001**	0.3872	0.827	(0.835–0.973)
CRI.I	90.4%	99%	82.70%	<0.001**	2.4388	0.827	(0.835–0.973)
CRI.II	97.8%	96%	90.40%	<0.001**	1.3042	0.904	(0.955–1.000)
C. index	98%	95%	92.30%	<0.001**	18.9	0.923	(0.957–1.000)

*= Non significant. **= Significant.

Figure 5



ROC curves for, atherogenic indices in nephrotic syndrome patients to analyze the optimal diagnostic points for predicting such cases compared to control group.

statistics were used to confirm the sensitivity and specificity of the results Fig. 5, Table 5.

Discussion

Pediatric renal diseases are associated with a significant rise in (CVD) risk. That means major kidney function deterioration may be predicted by lipid problems or an increased atherogenic index (AC, AIP, CRI.I, CRI.II, and C. index). Atherosclerosis and cardiovascular disease (CVD) have been linked closely to lipid abnormalities (such dyslipidemia) [9]. When monitoring early cardiovascular risk in children with NS, blood lipid ratios may be more useful than conventional blood lipid measures [10]. The atherogenic index of plasma (AIP), which is calculated as the logarithmically transformed ratio of triglyceride (TG) to high-density lipoprotein cholesterol (HDL-C) (lg[TG/HDL-C]), is a novel marker of atherosclerosis and (CVD). It has been reported that AIP is a better predictor of (CVD) than standard lipid measurements, the calculation of atherogenic index of plasma (AIP) can be readily derived from the typical lipid profile. In addition to individual lipids and the (TC/HDL-C) ratio, the measurement of lipoprotein particle size serves as a valuable predictor. [11]. Huang *et al.*, 2020 found that (AIP) was connected to the lipid complication in patients of nephrotic syndrome. AIP is a prediction of renal subclinical impairment, which is indicated by an eGFR between 30 and 60 ml/min/1.73 m^2 in recent research [12]. Also, the ratio of non-high-density lipoprotein cholesterol (non-HDL-C) to high-density lipoprotein cholesterol (HDL-C) is known as the atherogenic coefficient (AC). It has been utilized as a diagnostic option to foretell the likelihood of having cardiovascular events [13]. Furthermore, Castelli's risk indexes (I and II) are two lipid ratios that are both referred to as cardiac risk indexes. The CRI-I measures the proportion of TC to HDL-C, while the CRI- II measures the proportion of LDL-C to HDL-C, both have notably favorable relationships with CVD risk [14]. Many reports assessed and confirmed their positive correlation with CVD [15–17]. While, more accurately

Table 5 Receiver operating characteristic curve demonstrating accuracy, positive and negative predictive values of atherogenic indices in patients versus controls

Variable	PPV	NPV	Accuracy
AC	99%	94.12%	97%
AIP	91.5%	83%	87%
CRI.I	53.93%	63.64%	55%
CRI.II	95.92%	90.2%	93%
C. index	99%	96%	96%

NPV, Negative protective value; PPP, Positive protective value.

than the other indices, the cholesterol index (C. index) was described as a straightforward index that predicts the likelihood of developing coronary artery disease (CAD) [18]. Castelli risk index-1 (CRI-1), castelli risk index-2 (CRI-2), the atherogenic index of plasma AIP, the atherogenic coefficient (AC), and the cholesterol index were all considerably higher in the NS than they were in the control group (P=0.001). However, only a few investigations, like the one done by Smajic *et al.* in 2018, have demonstrated the potential clinical utility of (AIP) [8]. The mean variations in the atherogenic indices for potential confounders were the main focus of this investigation. Each index had a strong correlation with the onset of the nephrotic syndrome. In general, it is yet unknown how dyslipidaemia might speed up the progression of renal illness. One of the potential causes of dyslipidemia is an increase in the reabsorption of phospholipids and cholesterol by tubular epithelial cells. This reabsorption might then cause tissue damage, tubulointerstitial irritation, and foam cell development [19]. Additionally, higher amounts of lipoproteins may promote the production of pro-inflammatory cytokines, which would lead to glomerulosclerosis [20]. Increased levels of blood triglycerides, VLDL, IDL, and the triglyceride content of apoB-containing lipoproteins are all effects of nephrotic syndrome [21]. VLDL and chylomicron clearance are hindered, which results in these abnormalities [22]. The processes of chylomicron and (VLDL) maturation and removal, along with the appropriate lipid and apoprotein exchange between (HDL) and apoB-carrying lipoproteins, play integral roles in the formation of LDL in its typical state. The lipoprotein lipase (LPL) and hepatic lipase, along with its associated processes, are encompassed under this framework. Moreover, the lipoproteins undergo structural modifications that hinder their ability to efficiently engage with crucial receptors, trigger lipolytic enzymes, and facilitate the exchange of lipids and apoproteins with (HDL) [23].

On the other hand, it has also been suggested that aberrant (HDL) levels affect how (VLDL) and chylomicrons are metabolized. Lecithin cholesteryl ester acyltransferase (LCAT) insufficiency and (CETP) overexpression are caused by nephrotic syndrome, and these changes affect the maturation of cholesterol-poor HDL into cholesterol-rich HDL by increasing its triglyceride content and decreasing its cholesterol ester content. Due to a lack of (HDL), which is high in cholesterol, apoE and apoC can only contribute so much to developing (VLDL) and chylomicrons. As apoE and apoC are required for the binding of apoB-containing lipoproteins Aberrant (HDL) levels support the faulty (VLDL) metabolism in nephrotic syndrome via activation of LPL and endothelium [23]. Since it's been shown that animals with nephrotic syndrome had higher expression of the genes responsible for producing phospholipids and triglycerides in their livers [24]. Despite possible downregulation of genes encoding proteins involved in fatty acid catabolism in the liver, Nephrotic syndrome may result in increased expression of key enzymes involved in fatty acid biosynthesis, including acetyl coenzyme A (CoA) carboxylase, fatty acid synthase, and elongation of very long chain fatty acids 2 and 6 [25]. Others have proposed that these abnormalities, in addition to decreased clearance of triglyceride-rich lipoproteins and increased synthesis of fatty acids, triglycerides, and phospholipids, may be the cause of the hyperlipidemia in nephrotic syndrome [21]. The previously documented anomalies of lipid metabolism in nephrotic syndrome may have grave repercussions: Atherosclerosis and cardiovascular disease are exacerbated by the accumulation of chylomicron remnants and atherogenic (LDL, IDL, and IDL) in conjunction with a dysfunctional HDL-mediated reverse cholesterol transport; Body mass is decreased and exercise capacity is decreased due to decreased lipid transport to skeletal muscles and adipose tissue induced by lipoprotein lipase deficiency and malfunction [25]. In proximal tubular epithelial cells, the reabsorbed filtered albumin and other lipid-containing proteins lead to a buildup of lipids and cytotoxicity, which can lead to the loss of nephrons and the onset and progression of chronic kidney disease. Glomerular mesangial cell uptake of aberrant lipoproteins also encourages glomerulosclerosis. Additionally, raising the risk is a rise in plasma LP(a) in nephrotic individuals [23]. Similar to how dysregulated lipid metabolism and dyslipidemia are associated to all of these problems in (NS) patients, including the elevated risk of atherosclerosis and thromboembolism [26]. It was fully reflected in the rise in atherogenic index levels. Using the 'alternative lipid window,' dyslipidemia in the acute phase of (NS) can be quickly and easily understood. Particularly for patients with hyperlipidemia, it means that certain of those patients may be exposed to the danger of endothelial cell deterioration. By applying these criteria, it was discovered that the majority of (NS) patients have a high chance of getting vascular disease before their time [27,28]. From our perspective, these indices provide fresh information on the atherogenic

pathways in these situations, which might more accurately reflect the inflammatory signals than a lipid panel.

Conclusions

An attempt has been made in this investigation to identify the serum lipid profile in the nephrotic syndrome affected youngsters in Iraq, Kerbala. It has been established that hyperlipidemia in nephrotic patients increases their risk of developing cardiovascular disease. The 'alternative lipid window' of atherogenic indices, which may be easily obtained using standard biochemical measures, aids in understanding the hyperlipidemia of individuals with NS. In order to better manage patients with nephrotic syndrome, an argument was made for the use of these indices among the biochemical marks.

Declaration of patient consent: All necessary consent forms from patients have been received, as attested by the authors.

Author's contribution: The work's conception and design owe a great deal to everyone's contributions. All authors approved the final version for publication and agreed to be responsible for all parts of the work, including conducting adequate research to resolve any concerns about the accuracy or integrity of any portion of the work.

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Conflicts of interest

There are no conflicts of interest.

Declarations Ethics approval and consent to participate Ethical approval was received from the ethical and research committee of Department of bioChemistry, College of Medicine, University of Kerbala

Consent for publication Informed written consent was obtained from all the study participants.

Availability of data and material The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

There are no conflicts of interest.

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