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Soluble Urokinase Receptor and Echocardiographic Parameters in Children with Chronic Liver Diseases

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Abstract:

Background: Cardiomyocyte oedema and cardiac hypertrophy are among the significant health consequences of chronic liver diseases (CLD) in adolescents, which are experiencing rapid growth. Purpose: To evaluate soluble urokinase receptor (SuPAR) as a valuable marker for clinical cardiac dysfunction in children with CLD. **Methods:** This case-control study included two groups: CLD group: involved 48 children with CLD of different etiologies; and control group; involved 48 healthy children, matched for age and sex of studied group. All the participants were subjected to full history taking, clinical examination and laboratory investigations and liver biopsy, echocardiography and assessment of SuPAR by ELISA. **Results:** CLD group had statistically significant higher LVIDD, IVSD, LVPWD, LVMI, DT of mitral valve, E of tricuspid valve and statistically lower TAPSE compared to control group. CLD group had statistically significant higher suPAR compared to control group (91.9±31.3 vs 59.0±19.5 pg/ml), p<0.001.suPAR had a significant positive correlation with (ALT, AST, GGT, INR, total and direct bilirubin, liver span, spleen size, degree if fibrosis, HAI score, Aspartate aminotransferase to platelet ratio index (APRI) score and FIB-4) and statistically negative correlation with (hemoglobin and platelets). suPAR had a significant positive correlation with (LVIDD, IVSD, ICT of left ventricle), and had a significant negative correlation with (TAPSE, S of left ventricle, S, E of right ventricle). **Conclusion:** Children with CLD had significantly higher suPAR compared to healthy children. suPAR levels correlates positively with markers of liver disease severity and with echocardiographic changes.

Keywords: Soluble Urokinase Receptor; Echocardiographic; Chronic Liver Diseases; Soluble Urokinase Plasminogen Activator Receptor.

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Introduction

The chronic liver diseases (CLD) incidence in adolescents is increasing, leading to significant morbidity and mortality. The CLD is cirrhosis final stage, is characterised by the formation of a widespread nodule, vascular reorganisation, neo-angiogenesis, and the deposition of an extracellular matrix, all while disrupting liver architecture. At the cellular level, the recruitment of fibroblasts and stellate cells is the fundamental mechanism of fibrosis and cirrhosis, which induces fibrosis. Hepatic stem cells are indispensable for parenchymal cell regeneration [(1)].

In children with CLD, the liver biopsy is the superior method for assessing the severity of liver fibrosis and the progression of liver disease. Additionally, it is a critical tool for the management and decision-making of therapeutic interventions. Liver biopsy can lead to a range of complications, such as minor complications such as transient hypotension and pain, as well as major complications such as visceral perforation or significant haemorrhage, resulting in mortality [(2)].

The hyperdynamic circulation that is marked by lowering in systemic vascular resistance and low arterial blood pressure, as well as an increase in cardiac output and heart rate., is the primary cause of cardiac hypertrophy and cardiomyocyte oedema in patients with liver cirrhosis [(3)].

Cirrhotic cardiomyopathy is a term that refers to the structural and functional alterations of the myocardium. In the absence of other recognized cardiac disorders, chronic cardiac dysfunction in patients with cirrhosis is defined by impaired contractile responsiveness to stress, altered diastolic relaxation, and electrophysiological abnormalities [(4)].

Numerous active immunologically cells, such as activated T lymphocytes, neutrophils, and macrophages, as well as endothelial cells and podocytes, exhibit the soluble form of urokinase plasminogen activator receptor (suPAR). SuPAR is a membrane-bound protein. It is primarily produced by the enzymatic cleavage of the glycosylphosphatidylinositol anchor from the urokinase plasminogen activator receptor (uPAR). However, it exists as a secreted isoform as a result of alternative transcription. In numerous medical conditions that are linked to inflammation, such as diabetes ,kidney disease, smoking, sepsis, atherosclerosis, human immunodeficiency virus, heart failure, and autoimmune diseases, elevated levels of circulating suPAR are observed [(5)].

We aimed to investigate the SuPAR as a valuable indicator of clinical cardiac dysfunction in children with CLD.

Methods

This case-control study was conducted at Pediatric hepatology unit in Benha University Hospitals, Benha, Egypt, during the period from March 2022 to February 2025. The participants were divided into two groups: Group 1 (CLD group); included 48 children aged below 18 years with CLD of different etiology (HBV, HCV, Autoimmune and Metabolic Liver diseases) was confirmed by clinical examination, laboratory investigation and liver biopsy; they were CLD group included 25 females (54%) and 23 males (46%), their mean age was 9.8±3.1 years. Any patient with ischemic and non-ischemic cardiopathy, valvular heart diseases, congenital heart diseases, rhythm or conduction disorders or kidney diseases were excluded. Group 2 (Control group) (Healthy group); included apparently healthy 48 children, 28 males and 20 females, their average age was 9.2±3.3 years, matched for age and sex of studied group.

Each participant underwent a comprehensive clinical examination, complete history-taking, and laboratory evaluation of their complete blood count, liver function tests as ALT, AST, GGT, Alkaline phosphates, serum albumin, total bilirubin, and direct bilirubin, total immunoglobulin, coagulation profile (PT, PTT, INR) .

All patients underwent abdominal ultrasonography to assess the presence of ascites, splenic size, and liver size. The liver biopsy was performed on all patients using a modified Menghini aspiration instrument. A core that is adequate should contain a minimum of 10-12 portal tracts. The paraffin-embedded biopsy specimen was fixed in 10% formalin. The modified Ishak scoring system was employed to assess the histological activity of hepatitis by cutting five micrometer-thick sections, mounting them on a glass slide, and staining them with hematoxyline and eosin [(6)].

After undergoing a thorough baseline echocardiographic examination, the subsequent values were documented for each patient: In the parasternal long axis, M-mode echocardiography was employed to evaluate the LV end-systolic and end-diastolic dimensions, interventricular septal thickness, posterior wall thickness and LV ejection fraction. The apical four chamber view was employed to evaluate the mitral and tricuspid Doppler signals. The variables that were assessed included the mitral deceleration time of early filling (E-DT, millisecond), early diastolic peak velocity (peak E, cm/s), late diastolic peak velocity (peak A, cm/s), and early to late diastolic peak velocity ratio (E/A). The LVM was determined by dividing 0.8 by 1.04[(LVED + left ventricular (LV)posterior wall thickness + interventricular septal thickness)3 - LVED3] + 0.6. The equation for LVMI is achieved by dividing the body surface area by LVM. Using tissue Doppler imaging in an apical 4-chamber view, the longitudinal annular velocities (VEL) at the lateral mitral wall, septum, and lateral tricuspid wall, which are adjacent to the atrioventricullar valve hinge sites, were determined. In the lateral mitral, septal, and lateral tricuspid walls, isovolumetric contraction, relaxation periods, and systolic, early diastolic (Ea), and late diastolic (Aa) tissue Doppler velocities were assessed. Individual patients were assessed for their transtricuspid and transmitral E/Ea ratios. The myocardial performance index (MPI) is a measurement that assesses the myocardium's combined systolic and diastolic function. It is determined by adding the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) and dividing the sum by the ejection time (ET) for each ventricle.

The following scores were collected; APRI [(7)], The following formula is used to determine the fibrosis index based on four factors (FIB-4): FIB-4 = Age (years) × AST (U/L)/[PLT (109 L−1) × ALT1/2 (U/L)] [(8)]. Child-Pugh score; was conceptualized by Child and Turcotte in 1964 [(9)]. The PELD score (Paediatric End-stage Liver Disease, assigned to children under the age of 12) was employed for the youngest children. PELD = 4.80 [Ln serum bilirubin (mg/dL)] + 18.57 [Ln INR] - 6.87 [Ln albumin (g/dL)] + 6.67 (growth failure) + 4.36 (<1 year old) [(10)].

The MELD score (Model for End-Stage Liver Disease Score) was determined using the following formula:MELD = 3.78 [Ln serum bilirubin (mg/dL)] + 11.2 [Ln INR] + 9.57 [Ln serum creatinine (mg/dL)] + 6.43 [(11)].

Assessment of serum level of SuPAR using human suPAR ELISA Kit, Cat no . 201-12-5720, Company. Supplied By Shanghai Sunredbio(SRB) Technology co.,Ltd, Made in china.

Ethical considerations

The local ethics commission at the Faculty of Medicine at Benha University approved the entire study design. The study was conducted with the utmost respect for personal privacy and confidentiality. Guardians were permitted to disengage from the study at any time without incurring any repercussions. The data that was collected was not and will not be utilised for any other purpose.

Approval code: MS 21-8-2023

Statistical analysis

SPSS (version 24, IBM Corp., Armonk, NY, USA) was employed to code, input, and process the data on a computer. The results were subsequently presented in graphical and tabular formats to facilitate interpretation. The statistical metrics employed for the purpose of description were mean, standard deviation, range, and percentage. A significance level of 0.05 was employed to ensure that the results were deemed acceptable. If there is no statistical significance, a p-value greater than 0.05 is not significant. Testing was conducted in its entirety: The relationship factors in categorical data were examined using the Chi-Square test X^3. In a study that employed normal-distributing independent samples, the Students' t-test was implemented to determine whether there was a statistically significant difference between the means of two populations. In a study that included normally distributed, independent samples, researchers employed a one-way analysis of variance (ANOVA) to determine whether a difference in more than two population means was statistically significant. A linear relationship between two quantitative variables (X and Y, in this case) can be defined using the Spearman's correlation coefficient. The ROC, or receiver operator characteristic curve, illustrates the test's "sensitivity," which is defined as its ability to identify positive cases with minimal false negatives. A test's specificity is defined as its ability to identify positive cases with minimal false positives. Accuracy of a curve is quantified by the area under the curve (AUC) . If the area is greater, the curve is more precisely outlined. The yellow line serves as a line of reference that divides the space in half. AUC with a 95% confidence interval (CI): this is the range of values where the researcher has a 95% chance of discovering the true AUC.

Results

This study included 48 children with CLD and 48 healthy controls. In CLD group; the mean age at disease onset was 4.8±3.2 years, the mean disease duration was 5.4±2.9 years, the most common etiology of liver disease was glycogen storage disease (52.1%), followed by autoimmune hepatitis (20.8%), 35.4% of cases had abdominal distension, 33.4% had abdominal pain, 20.8% had jaundice, 27.1% had convulsions due to hypoglycemia. most cases (41.6%) had mild fibrosis, 18.8% had mild-moderate fibrosis and 16.6% had moderate fibrosis. Regarding HAI score; 45.8% of patients were minimal, 33.4% of patients were mild, and 10.4% were moderate and 10.4% were severe. Most cases had mononuclear inflammatory cells (54.2%), 29.2% had lymphocytes infiltrates. **Table 1**

CLD group had statistically significant higher LVIDD, IVSD, LVPWD, LVMI, DT of mitral valve, E of tricuspid valve and statistically lower TAPSE compared to control group. While there was An insignificant difference between groups as regard other echocardiography parameters. CLD group had statistically significant higher ICT, IRT, ET, MPI, E/Ea of left and right ventricles and statistically higher S wave, E wave of left and right ventricles compared to control group. Other tissue Doppler parameters were insignificantly different between both groups. **Table 2**

Fig. 1 shows suPAR in the studied groups. CLD group had a significant higher suPAR (91.9±31.3 pg/ml) compared to control group (59.0±19.5 pg/ml), p<0.001. suPAR levels increased significantly with higher grades of fibrosis and HAI score. While there was no statistical significant difference in suPAR levels as regarding to type of cells. **Table 3**

suPAR had a significant positive correlation with (ALT, AST, GGT, INR, total and direct bilirubin, liver span, spleen size, degree if fibrosis, HAI score, APRI score and FIB-4) and statistically negative correlation with (hemoglobin and platelets). suPAR had a significant positive correlation with (LVIDD, IVSD, ICT of left ventricle), and had a statistically significant negative correlation with (TAPSE, S of left ventricle, S, E of right ventricle). **Table 4**

The performance of suPAR in the detection of cases of CLD with mild to moderate fibrosis from controls was evaluated using ROC analysis; At a cutoff point ≥ 71.3 μg/mL ,AUC was 0.831 (95% CI: 0.750-0.911), the sensitivity was 83.3% and specificity was 70.2% p<0.001.**Fig. 2A**

The performance of suPAR in the detection of cases of CLD with severe fibrosis from controls was evaluated using ROC analysis; AUC was 0.991 (95% CI: 0.974-1), p<0.001. At a cutoff point ≥ 111.2 μg/mL, the sensitivity was 100% and specificity was 97.8%. **Fig.2B**

suPAR's ability to identify instances of cardiac dysfunction was evaluated through ROC analysis (with MPI>0.35); AUC was 0.939 (95% CI: 0.860-1), p<0.001. At a cutoff point ≥ 87.5 μg/mL, the sensitivity was 81.8% and specificity was 90.6%. **Fig. 2C**

Table 1: Clinical criteria of the studied patients

		CLD group N=48	**%**
Age at disease onset (years)	**Mean±SD**	4.8±3.2	
	Range	0.5-13	
Disease duration (years)	**Mean±SD**	5.4±2.9	
	Range	1-15	
Etiology of chronic liver disease	**Glycogen storage disease**	25	52.1%
	Autoimmune hepatitis	10	20.8%
	Wilson disease	4	8.4%
	Chronic hepatitis B	3	6.3%
	Chronic hepatitis C	5	10.4%
	Congenital hepatic fibrosis	3	6.3%
Presenting symptoms	**Abdominal distension**	17	35.4%
	Abdominal pain	16	33.4%
	Jaundice	10	20.8%
	Convulsions due to hypoglycemia	13	27.1%
Liver biopsy results in the studied group according to Ishak score			
Degree of fibrosis	**No fibrosis (F0)**	6	12.6%
	Mild (F1)	20	41.6%
	Mild to Moderate (F2)	9	18.8%
	Moderate fibrosis (F3)	8	16.6%
	Moderate to severe fibrosis (F4)	4	8.4%
	Incomplete cirrhosis (F5)	1	2.1%
	Cirrhosis (F6)	0	0.0%
	Mean ±SD (/6)	1.7±1.3	
	Range	0-5	
Histological activity index	**Minimal**	22	45.8%
	Mild	16	33.4%
	Moderate	5	10.4%
	Severe	5	10.4%
	Mean ±SD (/18)	4.8±2.9	
	Range	1-16	
Type of cells	**Loss of hepatic alrchitiure micro nodules of regeneration**	2	4.2%
	Lymphocytes	14	29.2%
	Lymphocytes and plasma cells	4	8.3%
	Eosinophils	1	2.1%
	Mononuclear inflammatory cells	26	54.2%
	paucity of bile ducts and lymphocytes infiltration	1	2.1%

Data are presented as mean ± SD or frequency (%).

Table 2: Echocardiography and tissue doppler of of the studied groups

		CLD group N=48	Control group N=48	Test	P value
Left ventricular function					
LVIDD (cm)	**Mean ± SD**	3.8±0.5	2.8±0.8	t=7.1	**<0.001***
	Range	2.8-4.8	1.7-4.4		
IVSD (cm)	**Mean ± SD**	0.7±0.1	0.6±0.2	t=5.1	**<0.001***
	Range	0.4-0.9	0.3-0.9		
LVPWD (cm)	**Mean ± SD**	0.6±0.1	0.5±0.1	t=4.8	**<0.001***
	Range	0.4-0.9	0.3-0.9		
LVMI (g/m^2)	**Mean ± SD**	39.4±11.2	31.6±10.1	t=4.2	**<0.001***
	Range	29.8-43.7	28.1-38.9		
EF (%)	**Mean ± SD**	73.0±7.2	73.7±8.1	t=0.47	0.63
	Range	63-88.7	61.9-86.8		
FS (%)	**Mean ± SD**	41.9±6.6	41.8±6.9	t=0.06	0.95
	Range	34-57.7	32-54.4		
Mitral valve					
E (cm/s)	**Mean ± SD**	100.3±15.2	102.3±15.2	t=0.64	0.52
	Range	75.7-125	75.4-119		
A (cm/s)	**Mean ± SD**	63.4±11.2	67.8±22.5	t=1.2	0.23
	Range	44-104	44.3-118		
E/A	**Mean ± SD**	1.6±0.26	1.6±0.32	t=0.23	0.81
	Range	1.1-2.1	1-2.1		
DT (ms)	**Mean ± SD**	131.8±17.7	115.3±27.3	t=3.3	0.001*
	Range	94-160	68-156		
Right ventricular function					
TAPSE	**Mean ± SD**	13.5±4.9	18.5±4.4	t=5.3	**<0.001***
	Range	4-21	11-26		
Tricuspid valve					
E (cm/s)	**Mean ± SD**	73.9±14.2	79.2±12.7	t=2	**0.045***
	Range	47.9-106	55.7-106		
A (cm/s)	**Mean ± SD**	60.3±15.6	60.2±14.8	t=0.05	0.95
	Range	36.6-101	37-101		
E/A	**Mean ± SD**	1.2±0.3	1.3±0.3	t=1.4	0.15
	Range	0.8-2.4	0.8-2.3		
DT (ms)	**Mean ± SD**	128.5±9.9	123.1±8.4	t=1.6	0.12
	Range	90-156	106-135		
Tissue Doppler					
S (cm/s)	**Mean ± SD**	7.9±1.4	9.2±1.5	t=4.3	**<0.001***
	Range	5.9-12.1	6.6-12.6		
E (cm/s)	**Mean ± SD**	11.9±2.9	13.2±2.8	t=2.1	**0.031***
	Range	6.9-16.9	7.7-17.6		
A (cm/s)	**Mean ± SD**	7.8±2.1	7.2±1.9	t=1.3	**0.19**
	Range	4.1-12	4.1-10.7		
ICT (ms)	**Mean ± SD**	48.1±8.2	41.6±10.3	t=3.2	**<0.001***
	Range	31-59	23-51		
IRT (ms)	**Mean ± SD**	52.0±7.2	47.1±6.8	t=3.4	**<0.001***
	Range	40-67	35-58		
ET (ms)	**Mean ± SD**	252.7±28.6	239±30.2	t=2.2	**0.025***
	Range	162-315	185-314		
MPI	**Mean ± SD**	0.46±0.14	0.36±0.13	t=2.1	**0.03***
	Range	0.31-0.68	0.29-0.5		
E/Ea	**Mean ± SD**	8.4±1.5	7.7±1.1	t=2.6	**0.006***
	Range	7.4-10.3	6.9-9.7		
Right ventricular					
S (cm/s)	**Mean ± SD**	9±2.1	11.6±2.7	t=7.2	**<0.001***
	Range	5.3-13	8-17		
E (cm/s)	**Mean ± SD**	13.1±3.2	15±2.7	t=3.1	**0.003***
	Range	9.8-19	10.2-20		
A (cm/s)	**Mean ± SD**	7.7±2.9	6.8±2	t=5.6	0.08
	Range	5.6-14.9	4.8-14.1		
ICT (ms)	**Mean ± SD**	49.4±7.4	41.1±8.9	t=3.2	**<0.001***
	Range	27-54	32-58		
IRT (ms)	**Mean ± SD**	49.5±7.6	45.3±9.3	t=2.3	**0.022***
	Range	27-63	31-58		
ET (ms)	**Mean ± SD**	369±34	239±30	t=4.6	**<0.001***
	Range	229-360	185-314		
MPI	**Mean ± SD**	0.48±0.15	0.38±0.11	t=2.6	**0.007***
	Range	0.32-0.67	0.29-0.61		
E/Ea	**Mean ± SD**	5.6±0.9	5.2±1.1	t=2.1	**0.021***
	Range	4.8-6.7	4.1-6.3		

Data are presented as mean ± SD or Median IQR. t: Student t-test, LVEDD: left ventricular end-diastolic dimension, IVSD; interventricular septal thickness end-diastolic, EF: Ejection fraction, LVPWD: left ventricular posterior wall dimension end-diastolic ,SF: shortening fraction; A - late diastole peak transmitral flow velocity; E - peak transmitral flow velocity in early diastole; E/A: early to late diastolic peak velocity ratio (E/A). TAPSE: Tricuspid annular plane systolic excursion. DT: deceleration time; LVMI: left ventricular mass index*: significant as P value ≤ 0.05.

Table 3: suPAR as regarding to results of liver biopsy

		suPAR (pg/ml) Mean ± SD	Min.	Max.	Test	P value
Fibrosis degree	**F0**	84.7±21.2	59.1	123.0	F=11.2	0.037*
	F1	79.9±19.0	46.9	143.3		
	F2	79.9±18.4	38.7	97.0		
	F3	94.2±28.6	64.0	159.0		
	F4	140.2±47.2	71.7	171.2		
	F5	159.5±1.1	156.7	173.2		
HAI score	**Minimal**	74.2±13.2	38.7	88.0	F=21.9	<0.001*
	Mild	83.3±11.6	62.0	99.1		
	Moderate	120.4±36.7	81.1	159.0		
	Severe	154.5±18.2	123.0	173.2		
Type of cells	**Loss of hepatic alrchitiure micro nodules of regeneration**	90.7±29.2	70.1	173.2	F=8.9	0.17
	Lymphocytes	81.2±19.0	46.9	143.3		
	Lymphocytes and plasma cells	84.9±25.7	38.7	156.7		
	Eosinophils	88.2				
	Mononuclear inflammatory cells	81.5±20.2	47.5	146.2		
	paucity of bile ducts and lymphocyts infiltraion	81.2				

Data are presented as mean ± SD. F: F value of one way ANOVA, , suPAR :Soluble urokinase plasminogen activator receptor *: significant as P value ≤ 0.05.

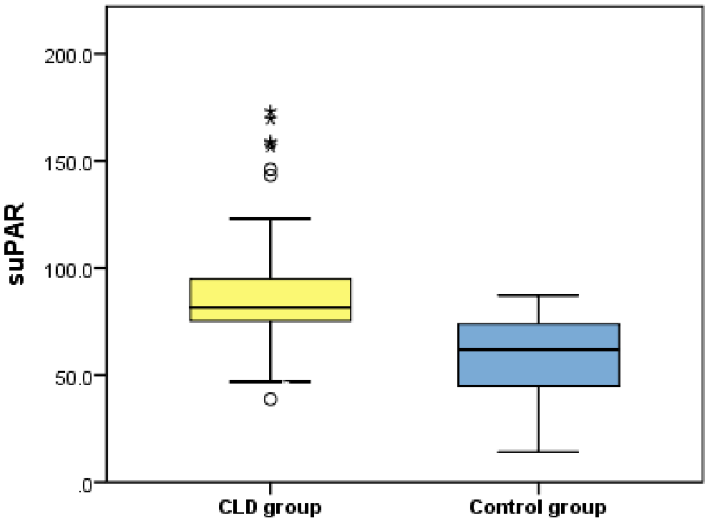
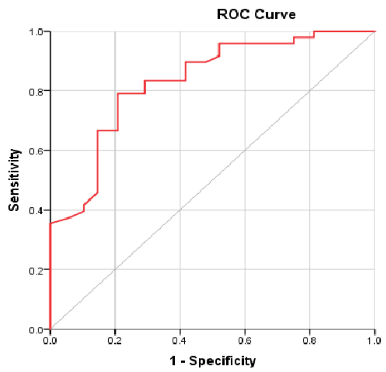


Fig. 1: Soluble urokinase plasminogen activator receptor (suPAR) in the studied groups.

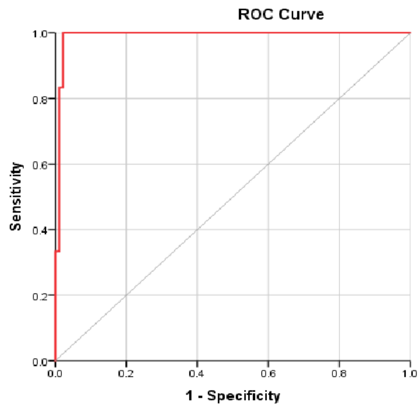
Table 4: Correlations between suPAR and patients' clinical data, echocardiography and tissue doppler parameters

		suPAR (pg/ml)	
		r	**P value**
Age (years)		0.119	0.249
Duration of liver illness (years)		0.092	0.536
Age at disease onset (years)		0.118	0.426
Weight percentile		-0.189	0.066
Height percentile		-0.006	0.953
BMI percentile		-0.146	0.155
Hemoglobin (mg/dl)		-0.473	**<0.001***
WBCs ($x10^3$ /L)		-0.002	0.983
Platelets ($x10^3$/L)		-0.313	**0.002***
AST (U/L)		0.373	**<0.001***
ALT (U/L)		0.402	**<0.001***
GGT (U/L)		0.440	**<0.001***
Serum albumin (g/dl)		-0.192	0.061
PT (sec.)		0.107	0.300
PTT (sec.)		0.179	0.080
INR		0.232	**0.023***
Total bilirubin (mg/dl)		0.229	**0.025***
Direct bilirubin (mg/dl)		0.323	**<0.001***
Liver span (cm)		0.435	**<0.001***
Spleen size (cm)		0.498	**<0.001***
Degree of fibrosis		0.567	**<0.001***
Hepatitis activity index score		0.833	**<0.001***
APRI Score		0.589	**<0.001***
FIB-4		0.556	**<0.001***
Child-Pugh		0.147	0.110
PELD		0.326	0.086
MELD		0.504	0.066
Echocardiography			
Left ventricular function	**LVIDD (cm)**	0.380	**<0.001***
	IVSD (cm)	0.331	**<0.001***
	LVPWD (cm)	0.319	**0.002***
	EF	0.014	0.895
	FS	0.041	0.689
Mitral valve	**E (cm/s)**	0.049	0.636
	A (cm/s)	-0.089	0.387
	E/A	-0.169	0.100
	DT (ms)	0.093	0.365
Right ventricular function	**TAPSE**	-0.275	**0.007***
Tricuspid valve	**E (cm/s)**	-0.222	**0.030***
	A (cm/s)	-0.104	0.315
	E/A	-0.026	0.799
	DT (ms)	0.222	**0.030***
Tissue Doppler			
Left ventricle	**S (cm/s)**	-0.229	**0.025***
	E (cm/s)	-0.149	0.150
	A (cm/s)	0.013	0.902
	ICT (ms)	0.247	**0.015***
	IRT (ms)	0.190	0.064
	ET (ms)	0.154	0.134
	MPI	0.115	0.266
Right ventricle	**S (cm/s)**	-0.439	**<0.001***
	E (cm/s)	-0.210	**0.040***
	A (cm/s)	0.158	0.091
	ICT (ms)	-0.113	0.273
	IRT (ms)	0.131	0.204
	ET (ms)	0.106	0.211
	MPI	0.212	0.058

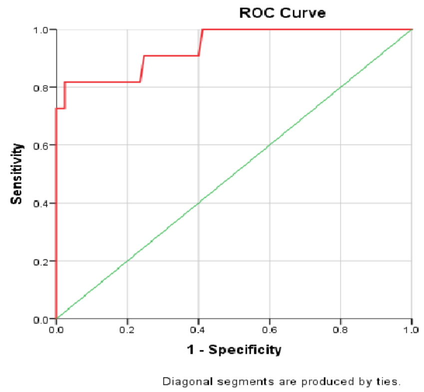
Data are presented as numbers. r: Correlation coefficient, WBCs: white blood cells, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT: Gamma Glutamyl Transferase, PT: prothrombin time, PTT: Partial thromboplastin time, INR: international normalized ratio, MELD: model end-stage liver disease, APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis index-4, PELD: pediatric end-stage liver disease,. LVEDD: left ventricular end-diastolic dimension, IVSD; interventricular septal thickness end-diastolic, LVPWD: left ventricular posterior wall dimension end-diastolic, SF: shortening fraction; EF: Ejection fraction A - late diastole peak transmitral flow velocity; E - peak transmitral flow velocity in early diastole;. DT: deceleration time; E/A: early to late diastolic peak velocity ratio ,TAPSE: Tricuspid annular plane systolic excursion., E: peak early mitral inflow Doppler velocities, S: S-wave pulmonary venous flow velocity systolic ,A: peak late mitral inflow Doppler velocities, e′ early diastolic annular myocardial velocity, a′ late diastolic annular myocardial velocity, IRT isovolumetric relaxation time, ICT isovolumetric contraction time, MPI: Myocardial performance index.*: significant as P value ≤ 0.05.



(A)



(B)



(C)

Fig.2: (A): ROC curve of performance of suPAR to detect cases of CLD with mild to moderate fibrosis from controls, (B): ROC curve of performance of suPAR to detect cases of CLD with severe liver fibrosis from controls, (C): ROC curve of performance of suPAR to detect cases of cardiac dysfunction.

Discussion

The initial definition of cirrhotic cardiomyopathy was established by the World Congress of Gastroenterology thirteen years ago. The criterion for cirrhotic cardiomyopathy was defined as the early detection of altered echocardiographic parameters to diagnose subclinical cardiac dysfunctions in liver cirrhosis patients in the absence of other prior diseases [12].

In patients with liver cirrhosis, the systemic circulation becomes hyperdynamic, as demonstrated by an increase in heart rate, cardiac output, and a decrease in vascular resistance. The term "cirrhotic cardiomyopathy" has been employed to characterise the cardiac dysfunction that is associated with it, which is distinct from alcoholic myocardial disease [(13)].

Additionally, the myocardium's structure and function are altered in cirrhotic patients as a result of hyperdynamic circulation, which is induced by circulating cardio-depressive constituents and vaso-dilators [(14)].

In the current study, CLD group had statistically significant higher LVIDD, IVSD, LVPWD, LVMI, DT of mitral valve, E of tricuspid valve and statistically lower TAPSE compared to control group. CLD group had statistically significant higher ICT, IRT, ET, MPI, E/Ea of left and right ventricles and statistically higher S wave, E wave of left and right ventricles compared to control group. Other tissue Doppler parameters were insignificantly different between both groups.

Our results were agreed with Fattouh et al., [(15)] who investigated the cardiac functions of cirrhotic children using serum brain natriuretic peptide and tissue Doppler imaging. The study included 52 cirrhotic patients and 53 healthy controls of the same age and sex. They reported that patients had a larger left atrium and right ventricle (RV) (P value 0.05) and a greater posterior wall thickness of the left ventricle (P value 0.04) than controls. The late atrial diastolic filling velocity (A) of tricuspid valve (TV) inflow was significantly increased ($P < 0.001$), and the ratios between the early diastolic filling velocity (E) and A wave velocity (E/A) of both mitral valve and TV inflow were lower ($P < 0.005$ and 0.0008, respectively). In patients, the late diastolic peak myocardial velocity (A') (P= 0.0003) and systolic velocity (S') of the RV (P =0.01) were significantly higher (P =0.008), and the MPI of both the LV and RV was significantly improved (P 0.001 and 0.01).

This was in agreement with Junge et al., [(16)] in 198 children with CLDs who underwent liver transplantation, who examined the impact of paediatric cirrhotic cardiomyopathy on liver transplant outcomes. The z-score of the LV end-diastolic diameter [LVIDd], the left ventricular mass, and the LV mass index were significantly higher in cirrhotic patients (P=0.000, P=0.001, and P=0.001, respectively) than in non-cirrhotic liver disease children, as per their report. Pathological z-scores (>2SDS) for the LVIDd in cirrhotic patients were significantly associated with cholestasis, and they occurred more frequently than in patients with non-cirrhotic liver disease (31/169 vs. 1/29; P=0.03).In the year following the transplant, all cardiac modifications that were observed were reversible.

Similarly with our results Khemakanok et al., [(17)] conducted research on 20 cirrhotic infants cirrhotic infants both before and after liver transplantation, The majority of patients (75%) had decompensated cirrhosis and biliary atresia. Tragically, two patients passed away after the transplant. At 1-2 months and 3-6 months post-LT, echocardiography was re-evaluated in 17 and 18 patients, respectively. Most patients had cardiac abnormalities prior to transplantation, such as LV enlargement (50%), increased LV mass (95%), aberrant LV geometry (95%), hyperdynamic LV systolic function (60%), LV diastolic dysfunction (60%), and a high cardiac index (75%). At 3-6 months post-LT, no significant reduction in cardiac abnormalities was observed; however, cardiac parameters, such as LV dimension in diastole index and z-score, relative wall thickness, LV mass index and all experienced a substantial decrease.

Additionally, Rohani et al., [(18)] study of cardiopulmonary complications in cirrhotic paediatrics with contrast echocardiography on 22 children revealed that 27.3% of the patients had moderate LV diastolic dysfunction.

Thirteen years ago, the term "cirrhotic cardiomyopathy" was initially defined at the World Congress of Gastroenterology. The early detection of altered echocardiographic parameters to diagnose subclinical cardiac dysfunctions in liver cirrhosis patients was established as the criterion for cirrhotic cardiomyopathy in the absence of other prior diseases [(12)].

Liver cirrhosis patients' systemic circulation becomes hyperdynamic, defined by a decrease in vascular resistance and an increase in heart rate, cardiac output. A distinct condition from alcoholic myocardial disease is cirrhotic cardiomyopathy, which is the term used to describe the cardiac dysfunction that is associated with it [(13)].

Furthermore, the hyperdynamic circulation associated with the altered structure and functions of the myocardium in cirrhotic patients is exacerbated by circulating vaso-dilators and cardio-depressive constituents [(14)].

In the present study, CLD group had statistically significant higher suPAR compared to control group (91.9±31.3 vs 59.0±19.5 pg/ml).

To the best of our knowledge no previous studies assessment suPAR in children with CLD. Nevertheless, previous investigations on adults have demonstrated a gradual increase in circulating suPAR levels in a variety of chronic and acute liver diseases [(19)].

Manshad AS et al., [(20)], who studied kinetics of suPAR in cirrhosis, on 105 liver cirrhotic patients, suPAR concentration in those patients was significantly higher than the suPAR levels of healthy controls (*p*-values <0.001).

This was in agreement with Zimmermann et al., [(21)], The author of the study found that circulating suPAR levels were substantially higher in 159 participants with chronic liver disease compared to healthy controls (P < 0.001).

Currently, the cause of higher serum suPAR concentrations in CLD patients is unknown. Certain hypotheses could account for the elevated circulating uPAR in patients with CLD. Initially, the elevated circulating uPAR may be attributed to the release of uPAR in the injured liver. Secondly, the increase in circulating uPAR may be attributed to the imbalance between uPAR synthesis and uPAR clearance. The elevated circulating uPAR may be attributed to the reduction of uPAR destruction in CLD patients with hepatic fibrosis. A reduction in pre-systemic hepatic metabolism may be the cause of the elevated uPAR levels in serum BA children with hepatic dysfunction. Additionally, uPAR may be synthesised and released into the bloodstream by tissues other than the liver. The progression of liver fibrosis and hepatocellular injury is the most probable cause of the elevated serum level of uPAR. In CLD patients, the extent to which the increase in serum uPAR suggests low destruction, high production, or both remains uncertain. In order to elucidate the molecular mechanism that produces an increase in circulating uPAR, further research will be required [(22)].

We found that, suPAR had a significant positive correlation with (LVIDD, IVSD, ICT of LV), and had a significant negative correlation with (TAPSE, S of LV, S, E of right ventricle).

There is deficiency in studies about suPAR correlations with echocardiography or tissue Doppler in children with CLD. However, our results run in accordance with adults studies as Wlazeł et al., [(23)], according to whom the suPAR level was significantly increased in the LVH group (p = 0.033) and was correlated with cardiac diastolic function parameters in elderly individuals.

However, Manshad et al., [(20)], it was reported that suPAR was the sole biomarker linked with global longitudinal strain (GLS) (p = 0.009). suPAR was also correlated with the diastolic parameters A velocity (p = 0.017), E velocity (p = 0.018), and E/E' ratio (p = 0.033). In lung cancer patients, suPAR was not correlated with LVEF (p = 0.916).

Theilade et al., [24], SuPAR levels were not found to be correlated with EF (P=0.11). The diastolic measures a' and e'/a' were also impaired (P=0.034), and the systolic function was assessed using GLS and tissue velocity s'. Additionally, increased suPAR levels were independently associated with those measures.

Nevertheless, a mechanistic role for suPAR in cardiovascular diseases (CVD) has not been acknowledged.Compared to conventional markers of inflammation, such as high sensitivity C-reactive protein, suPAR is more effective in predicting a variety of CVD as an indicator of cardiovascular health. The primary function of inflammation in CVD suggests that suPAR may be beneficial in the prediction and prevention of cardiac disease, particularly in the high-risk population [20].

Conclusion

This investigation identified echocardiographic alterations in children with CLD. This is the reason why liver disease patients should undergo echocardiography to prevent the underdiagnosis of liver disease-related cardiomyopathy and to assure a more favourable prognosis. We suggested that suPAR is a component of the inflammatory process that leads to CLD. Echocardiographic alternations were also observed in those neonates. This requires further investigation to ascertain the source of suPAR in this population. Finally, this unique study highlightened the possible role of urokinase in early detection of cardiac abnormalities in children with CLD. So further larger studies are warranted to approve these results and further assessment about the benefits of these results to prevent cardiomyopathgy in CLD patients.

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Author contributions:

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