Correlation of Albuminuria and Renal Doppler Indices with Myocardial Function in Patients with Nephrotic Syndrome

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Abstract

Background: Nephrotic syndrome (NS) is characterized by proteinuria and edema, often stemming from minimal change disease. Secondary causes include systemic conditions and medications. NS raises the cardiovascular risk due to inflammation, cytokine release, hypoalbuminemia, and impaired cardiac function. Renal Doppler ultrasound evaluates the renal microcirculation using resistive index (RI) and pulsatility index (PI).

Objectives: To evaluate the impact of albuminuria and renal Doppler indices on myocardial function in patients with nephrotic syndrome, for early detection of myocardial dysfunction using speckle tracking echocardiography and renal Doppler imaging.

Patients and methods: This cross-sectional study was carried out at Qena University Hospitals, involving 100 participants: 60 patients with nephrotic syndrome and hypoalbuminemia and 40 control cases. Clinical, laboratory, and imaging assessments, including echocardiography and renal Doppler, were performed. Left ventricular ejection fraction (LVEF), global longitudinal strain (GLS), E/e' ratio, resistive index (RI), and pulsatility index (PI) were measured.

Results: The nephrotic group exhibited lower LVEF (63.3% versus 66.6%, $p < 0.01$) and GLS (-14.5 % versus -19.5 %, $p < 0.001$), along with an elevated E/e' ratio (7.15 versus 5.79, $p < 0.01$) compared to controls. Significant negative correlations were found between GLS and renal Doppler indices (RI and PI) ($p < 0.001$). Significant negative correlations were found between GLS and albumin creatinine ratio (ACR) ($p = 0.0195$).

Conclusion: Albuminuria and impaired renal microcirculation negatively affect myocardial function in nephrotic syndrome. Early detection of myocardial dysfunction using echocardiography and renal Doppler is crucial for better cardiovascular risk management in these patients.

Keywords: Renal Resistive Index; Pulsatility Index; Myocardial Function; Global Longitudinal Strain; Nephrotic Syndrome.

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Introduction

Nephrotic syndrome (NS) is a clinical disorder featured by significant proteinuria, hypoalbuminemia, and edema. It results from a variety of underlying etiologies, with minimal change disease (MCD) being the predominant cause, especially in children. MCD typically responds well to corticosteroid therapy and has a good prognosis, with minimal progression to chronic kidney disease (CKD). However, other forms of primary nephrotic syndrome, such as focal segmental glomerulosclerosis (FSGS), have a more variable prognosis, often progressing to CKD in the absence of effective treatment. Secondary nephrotic syndrome can arise from extrarenal conditions, including systemic diseases such as diabetes, lupus, and infections, or as a consequence of drugs and toxins **(Rodriguez and Adam, 2022)**.

Beyond renal complications, nephrotic syndrome is closely linked to increased cardiovascular morbidity and mortality. Patients with nephrotic syndrome exhibit a higher occurrence of cardiovascular illness compared to the general population. Several pathophysiological mechanisms contribute to this heightened cardiovascular risk, including hypercoagulability, dyslipidemia, and the activation of inflammatory and fibrotic pathways. The chronic inflammatory state observed in NS, with elevated levels of cytokines such as TNF-α and interleukins, plays a significant role in promoting vascular and myocardial dysfunction **(Çap et al., 2023).**

Furthermore, albuminuria and hypoalbuminemia, hallmarks of NS, contribute to fluid retention and edema, which in turn induces changes in both the cardiovascular and renal systems **(Kamel et al., 2021).**

One of the less understood yet important factors affecting cardiovascular health in NS patients is renal microcirculatory dysfunction. Renal Doppler ultrasonography, a non-invasive imaging technique, can be used to assess renal vascular resistance through indices such as the resistive index (RI) and pulsatility index (PI). These indices reflect changes in renal blood flow and resistance, offering valuable insights into both renal and systemic vascular health. Impaired renal microcirculation, as indicated by increased RI and PI, may contribute to elevated systemic vascular resistance, which in turn affects myocardial function. Renal Doppler is particularly useful in assessing patients with nephrotic syndrome, as changes in renal microcirculation often precede overt renal or cardiac dysfunction **(Bellos and Pergialiotis, 2020).**

In addition to these clinical parameters, the assessment of myocardial function in NS patients has gained importance in recent years. Speckle tracking echocardiography offers a novel, sensitive method for detecting subclinical cardiac dysfunction by measuring global longitudinal strain (GLS). GLS has emerged as a more reliable indicator of myocardial performance, even in the absence of overt structural changes or reduced ejection fraction (EF). In nephrotic syndrome, subclinical myocardial dysfunction may develop early, even before clinically evident heart failure, making early detection crucial for improving patient outcomes **(Çap et al., 2023).**

The primary aim of our research is to explore the correlation between albuminuria, renal Doppler indices, and myocardial function in patients with nephrotic syndrome. By utilizing speckle tracking echocardiography alongside renal Doppler imaging, we aim to identify early indicators of myocardial dysfunction, allowing for more timely interventions in this high-risk population.

Patients and methods:

This cross-sectional case-control study was carried out at internal medicine department, Qena University Hospitals from December 2023 to May 2024.

Inclusion criteria: Age: 18 years or older who has a diagnosis of nephrotic syndrome with hypoalbuminemia (serum albumin level < 2.5 gm/dl) and nephrotic range proteinuria.

Exclusion criteria: Normal serum albumin level, normal urine analysis or

microalbuminuria. Myocardial systolic dysfunction.

Study Protocol

•***Detailed history and clinical assessment*** were performed. Vital signs (blood pressure, heart rate, respiratory rate) and body mass index (BMI) were evaluated.

•***Laboratory Investigations****:* Complete Blood Count (CBC), renal function tests [serum creatinine, BUN, Glomerular Filtration Rate (GFR)], urine analysis and albumin/creatinine ratio (ACR). Regarding Laboratory Investigations: 10 ml of venous blood was drawn under aseptic conditions, using sodium citrate and EDTA tubes for blood sampling, and then 6 ml of the sample was coagulated, and then centrifuged at 3500 rpm to obtain serum for testing.

•***Echocardiography:*** Echocardiographic evaluation was done via a GE Vivid E95 ultrasound system (GE Healthcare, Chicago, IL, USA). Left ventricular ejection fraction (LVEF) was measured, and the E/e' ratio was measured using Doppler flow and tissue Doppler imaging. Global longitudinal strain (GLS) was calculated from multiple LV segments. All studies were electrocardiogram (ECG) gated and matching the American society of echocardiography recommendations **(Mitchell et al., 2019).**

•***Renal Doppler:*** Renal Doppler ultrasonography was done via a LOGIQ P7 ultrasound system (GE Healthcare, Chicago, IL, USA) with a 6–10 MHz transducer. Bilateral renal arteries were evaluated in various patient positions, assessing renal resistive index (RI) and pulsatility index (PI). Measurements were taken from multiple segments of the renal arteries, with Doppler range gate positioning at near-zero angles for accuracy **(Sawchuk et al., 2022).**

Sample Volume Calculation: A total of 100 individuals were studied, including 60 with nephrotic syndrome and 40 healthy controls. The sample size was calculated to ensure 95% confidence and 80% power based on prior studies of hypoalbuminemia and myocardial dysfunction.

Ethical approval: Following approval by the Ethical Board of the Faculty of Medicine, South Valley University, informed written consent was attained from all participants. Ethical approval Code: (SVU/MED/MED018/1/23/6/658). The research protocol tracked the ethical rules of the 1975 Declaration of Helsinki.

Statistical analysis

Data were gathered and evaluated using IBM SPSS version 27, with categorical variables expressed as numbers and percentages and numerical variables as means and standard deviations. Normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Fisher exact test was used for categorical comparisons, while independent t-tests assessed parametric data. Pearson correlation evaluated relationships between renal Doppler and echocardiography findings. A p-value < 0.05 was approved significant, with $p < 0.01$ indicating high significance.

Results

Demographics: The study included 60 nephrotic patients and 40 control cases. The mean age of participants was 33.9 ± 8.8 years, with 48% of participants being male. Nephrotic patients had a significantly higher BMI (26.4 ± 2.0 kg/m²) compared to controls (22.1 ± 1.3 kg/m², $p < 0.001$), **Table.1& 3).**

Clinical features: Edema was present in 66.6% of nephrotic patients, and 33.3% exhibited eye puffiness, (**Table.2).**

Laboratory results: The albumin creatinine ratio (ACR) was significantly higher in nephrotic patients (8292.2 ± 4380.1 mg/g versus 18.575 ± 5.737 mg/g). Hemoglobin levels were significantly lower in nephrotic patients (11.1 ± 1.3 g/dL versus 14.5 ± 0.9 g/dL, $p < 0.001$), as were white blood cell counts ($7.4 \pm 1.8 \times 10^9$/L versus $8.4 \pm 2.0 \times 10^9$/L, $p = 0.018$), **(Table.4).**

Echocardiographic findings: Nephrotic patients exhibited reduced left ventricular ejection fraction (LVEF %) (63.3% versus 66.6%, $p < 0.01$) and global longitudinal strain (GLS %) (-14.5 versus -19.5, $p < 0.001$), alongside a higher E/e' ratio (7.15 versus 5.79, $p < 0.01$), (**Table .5).**

Renal Doppler Findings: Nephrotic patients had higher RI and PI compared to controls ($p < 0.001$), **(Table .6).**

Correlations: GLS and RI: A significant negative correlation was found between GLS and RI across renal segments ($p < 0.001$, $r = -0.433$ to -0.444). **LVEF and RI:** A weak negative correlation was observed between LVEF and RI in several renal segments ($p < 0.01$, $r = -0.256$ to -0.375). **GLS and PI:** Strong negative correlations were found between GLS and PI in multiple renal segments, with the right upper segment showing the strongest correlation ($p < 0.001$, $r = -0.608$). **LVEF and PI:** Moderate negative correlations were found between LVEF and PI in the right middle segment ($p < 0.001$, $r = -0.438$). **GLS and ACR:** Negative correlations were found between GLS and ACR ($r = -0.3010$ $P = 0.0195$), **Tables (7& 8) and Figs 1-3). Fig.4** demonstrates a selected case.

Table 1. Demographic features of study participants (N=100)

Parameters		**Frequency**	**Percentage** (%)
Age (years)	**<30**	32	32%
	30-40	43	43%
	>40	25	25%
	Mean ± SD	33.90 ± 8.824	
	Median (range)	33 (19-54)	
Gender	**Male**	48	48 %
	Female	52	52 %
Body mass index (Kg/m^2)	**Healthy weight**	58	58%
	Overweight	41	41%
	Obese	1	1%
	Mean ± SD	24.6895 ± 2.72525	
	Median (range)	24.250 (20.20 – 31.25)	

Table 2. Clinical features of nephrotic cases (N=60)

Parameters		**Frequency**	**Percentage** (%)
Edema	Yes	40	66.6%
Eye puffiness	Yes	20	33.3%

Table 3.Demographic data of the studied groups

Parameters		**Nephrotic cases** (N=60)			**Controls** (N= 40)			**P-value**
		N	%	Mean ± SD	N	%	Mean ± SD	
Age (Years)				33.7 ± 9.9			34.08 ± 6.8	0.863
BMI (kg/m^2)				26.3 ± 2.0			22.135 ± 1.2	< 0.001**
BMI categories	**Healthy**	18	30		40	100		< 0.001*
	Overweight	41	68.33		0	0		
	Obese	1	1.67		0	0		
Gender (N & %	**Male**	27	45		21	52.5		0.462
	Female	33	55		19	47.5		

*Significant; *Fisher's exact test; ** student t-test; BMI, body mass index.

Table 4. Impact of nephrotic syndrome on CBC parameters

Complete blood count	Nephrotic cases (n=60)	Controls (n=40)	P-value
	Mean ± SD	Mean ± SD	
Hemoglobin (g/dL)	11.067 ± 1.3368	14.497 ± 0.9110	<0.001*
RBCs (*10^{12}/L)	5.023 ± 0.5160	4.855 ± 0.5099	0.112
WBCs (*10^{9}/L)	7.418 ± 1.8136	8.348 ± 1.9946	0.018*
Platelets (*10^{9}/L)	258.88 ± 58.755	261.02 ± 65.335	0.865

*Significant; *student t-test; RBCs, Red Blood Corpuscles; WBCs, White Blood Corpuscles.

Table 5. Impact of nephrotic syndrome on myocardial function (n=100)

Echocardiography Mean ± SD	Nephrotic cases (n=60)	Controls (n=40)	P-value
Left ventricular ejection fraction (%)	63.25 ± 4.003	66.60 ± 3.485	<0.001*
E/e´ ratio	7.148 ± 2.0223	5.792 ± 0.7777	<0.001*
Global longitudinal strain (%)	-14.475 ± -1.8442	-19.488 ± -2.2057	<0.001*

*Significant; student t-test; E/e´ ratio: ratio between early mitral inflow velocity and mitral annular early diastolic velocity.

Table 6. Impact of nephrotic syndrome on renal resistive index and renal pulsatility index

Renal Doppler	Nephrotic Cases (N = 60)	Controls (N = 40)	P-value
Renal resistive Index			
RUS	0.84 ± 0.15	0.63 ± 0.02	<0.0001*
RMS	0.65 ± 0.27	0.62 ± 0.03	0.0003*
RLS	0.77 ± 0.15	0.63 ± 0.02	<0.0001*
LUS	0.82 ± 0.16	0.62 ± 0.03	<0.0001*
LMS	0.81 ± 0.16	0.61 ± 0.03	<0.0001*
LLS	0.81 ± 0.14	0.62 ± 0.03	<0.0001*
Pulsatility Index			
RUS	1.73 ± 0.42	1.01 ± 0.02	<0.0001*
RMS	1.78 ± 0.37	1 ± 0.02	<0.0001*
RLS	1.8 ± 0.34	1.26 ± 1.56	<0.0001*
LUS	1.68 ± 0.44	1.01 ± 0.05	<0.0001*
LMS	1.72 ± 0.43	0.99 ± 0.14	<0.0001*
LLS	1.79 ± 0.37	1 ± 0.02	<0.0001*

*Significant; t-student test; RUS: right upper segment; RMS: right middle segment; RLS: right lower segment; LUS: left upper segment; LMS: left middle segment; LLS: left lower segment.

Table 7. Correlation between echocardiography parameters and renal Doppler (Renal arterial resistive index)

Renal Doppler (RI)	Echocardiography parameters					
	LVEF (%)		E/e´ ratio		GLS (%)	
	r	P-value	r	P-value	r	P-value
RUS	-0.375	<0.001*	0.119	0.239	-0.433	<0.001*

RMS	-0.149	0.138	-0.139	0.167	-0.083	0.412
RLS	-0.355	<0.001*	-0.005	0.957	-0.414	<0.001*
LUS	-0.256	0.010*	0.243	0.015*	-0.421	<0.001*
LMS	-0.312	0.002*	0.188	0.061	-0.444	<0.001*
LLS	-0.194	0.053	0.298	0.003*	-0.422	<0.001*

*Significant; r: Pearson correlation coefficient; RUS: right upper segment; RMS: right middle segment; RLS: right lower segment; LUS: left upper segment; LMS: left middle segment; LLS: left lower segment; LVEF: left ventricle ejection fraction; GLS: Global Longitudinal Strain; RI: resistive Index; E/e´ ratio: ratio between early mitral inflow velocity and mitral annular early diastolic velocity.

Table 8. Correlation between echocardiography parameters and renal Doppler (pulsatility index)

Renal Doppler (PI)	**Echocardiography parameters**					
	LVEF (%)		**E/e´ ratio**		**GLS (%)**	
	r	**P-value**	**r**	**P-value**	**r**	**P-value**
RUS	-0.373	<0.001*	0.204	0.042*	-0.608	<0.001*
RMS	-0.438	<0.001*	0.057	0.571	-0.569	<0.001*
RLS	-0.152	0.131	0.037	0.715	-0.235	0.019*
LUS	-0.215	0.032*	0.261	0.009*	-0.491	<0.001*
LMS	-0.274	0.006*	0.299	0.002*	-0.562	<0.001*
LLS	-0.389	<0.001*	0.130	0.197	-0.552	<0.001*

*Significant; r: Pearson correlation coefficient; RUS: right upper segment; RMS: right middle segment; RLS: right lower segment; LUS: left upper segment; LMS: left middle segment; LLS: left lower segment; LVEF: left ventricle ejection fraction; GLS: Global Longitudinal Strain; RI: resistive Index; E/e´ ratio: ratio between early mitral inflow velocity and mitral annular early diastolic velocity.

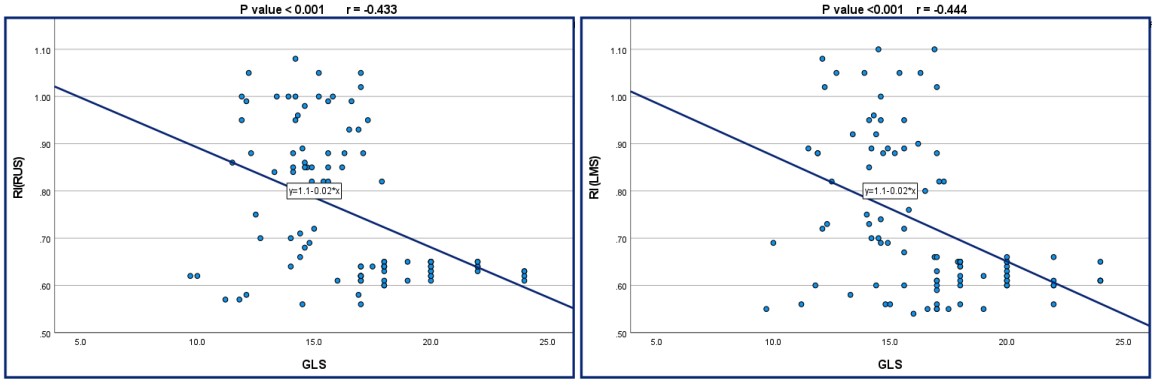


Fig. 1. Correlation between GLS on echocardiogram and RI in the right upper segment (RUS) and RI in the lower middle segment (LMS).

GLS, Global Longitudinal Strain, RI: resistive Index

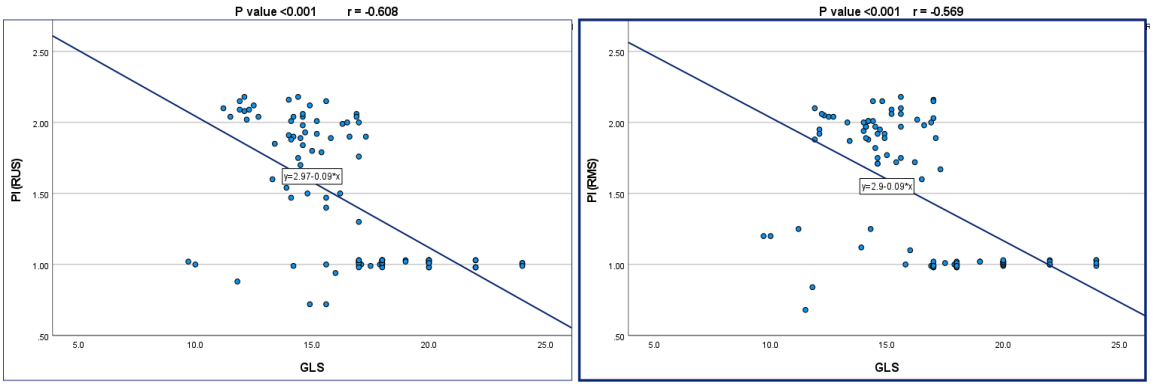


Fig.2. Correlation between GLS on echocardiogram and PI in the right upper segment (RUS) and PI in the right middle segment (RMS).

GLS: Global Longitudinal Strain, PI: Pulsatility Index

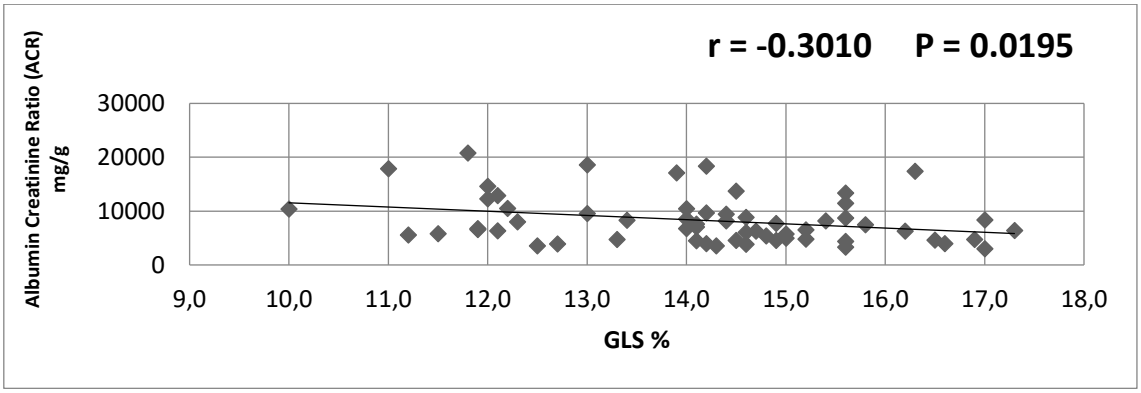
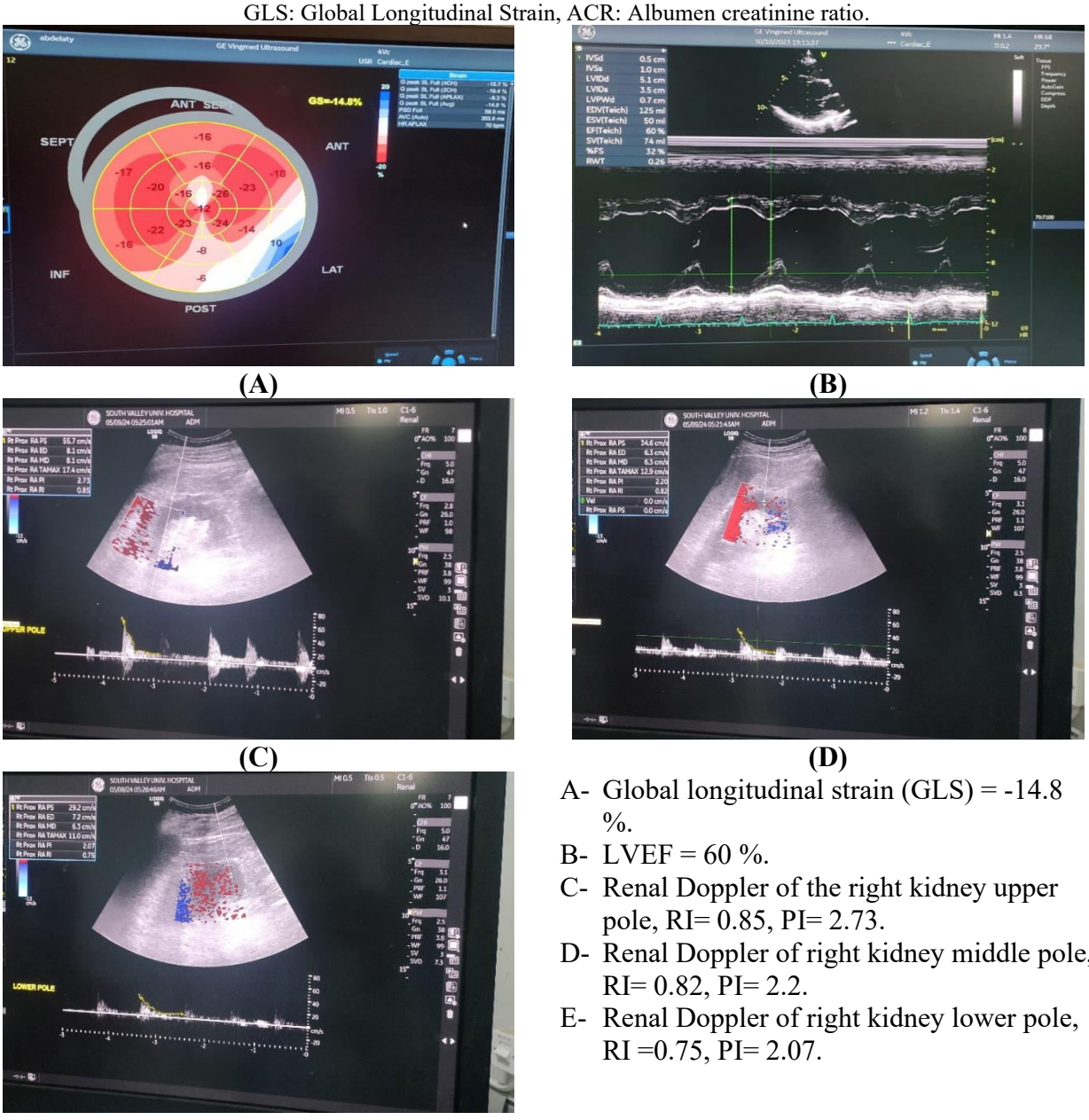


Fig. 3. Correlation between GLS on echocardiogram and ACR.

GLS: Global Longitudinal Strain, ACR: Albumen creatinine ratio.



A- Global longitudinal strain (GLS) = -14.8 %.
B- LVEF = 60 %.
C- Renal Doppler of the right kidney upper pole, RI= 0.85, PI= 2.73.
D- Renal Doppler of right kidney middle pole, RI= 0.82, PI= 2.2.
E- Renal Doppler of right kidney lower pole, RI =0.75, PI= 2.07.

Fig.4. Echocardiography and Renal Doppler of a 22-year-old male patient with nephrotic syndrome, not known for diabetes or hypertension, presented with eye puffiness and bilateral mild lower limb edema, labs (Albumin creatinine ratio = 5412 mg/g, urine albumin +2, and serum creatinine = 0.85 mg/dl). Patient Echocardiography and Renal Doppler;

Discussion

Nephrotic syndrome is known for its associations with various cardiovascular complications, which may be exacerbated by hypoalbuminemia and impaired renal function. This study investigated the link between albuminuria, renal Doppler indices, and myocardial function. Nephrotic patients had a higher mean BMI than controls (26.39 ± 2.01 kg/m² vs. 22.14 ± 1.25 kg/m², $p < 0.001$), likely due to fluid retention from hypoalbuminemia causing edema and weight gain. Additionally, chronic inflammation and cytokine activity associated with nephrotic syndrome may contribute to increased fat deposition, further raising BMI. Steroid therapy, commonly used to treat nephrotic syndrome, can also cause weight gain through increased appetite and fluid retention, exacerbating this association. These mechanisms collectively explain the observed higher BMI in nephrotic patients. Our study findings align with **(Göknar et al., 2022; Claudio and Gabriella, 2023).**

Our study findings are supported by **Shah et al. (2021)** who found obesity to be related to greater cardiovascular risk and lower proteinuria remission in nephrotic syndrome.

Nephrotic cases had lower hemoglobin, likely due to reduced erythropoietin, chronic inflammation, and increased hepcidin. Lower WBC counts may result from proteinuria and corticosteroid treatment. RBC and platelet levels remained unaffected, indicating nephrotic syndrome primarily impacts hemoglobin and WBCs. Our study findings support these observations and match with previous studies **(Pani, 2013; Iorember and Aviles, 2017; Campbell and Thurman, 2022)**.

Albuminuria and hypoalbuminemia in nephrotic syndrome are linked to impaired myocardial function. Nephrotic patients showed reduced GLS and LVEF, indicating subclinical systolic dysfunction from chronic inflammation and oxidative stress. An elevated E/e' ratio suggests diastolic dysfunction from fluid overload. Negative correlations were found between ACR and GLS suggesting that more severe albuminuria negatively affect myocardial mechanics. These findings highlight systolic and diastolic dysfunction in nephrotic syndrome, consistent with other studies (**Nalcacioglu et al., 2020; Podkowińska and Formanowicz, 2020; AbdelMassih et al., 2023; AbdelMassih et al., 2021)**.

Our study found significant correlations between elevated RI and PI with reduced GLS and LVEF, indicating myocardial dysfunction. Elevated RI and PI reflect impaired renal microcirculation, contributing to cardiovascular stress through fluid overload, RAAS activation, and increased vascular resistance. These factors lead to diastolic dysfunction, as shown by higher E/e' ratios in nephrotic patients. Our study findings are consistent with **AbdelMassih et al. (2021)** who reported higher LV E/e′ and reduced LV GLS in nephrotic cases compared to controls.

Our study findings are consistent with **Dey and Hage (2021),** who linked lower serum albumin to higher RI in nephrotic syndrome. They observed mean serum albumin levels of 1.82 ± 0.32 g/dL and RI values of 0.63–0.71 in renal poles, highlighting the role of hypoalbuminemia in renal vascular resistance and cardiovascular risk.

In contrast, **Tsai et al. (2011)** observed no notable alterations in renal vascular resistance among different albuminuria levels and noted no correlation between albuminuria and RI. These findings disagree with our study results, where we observed significant differences related to albuminuria.

Limitations: This study highlights the link between renal function and myocardial performance but is limited by relative small sample size and its cross-sectional design. Longitudinal studies are required to confirm causality and assess

early interventions. Future research should also examine the impact of comorbidities like hypertension and diabetes on cardiac function in nephrotic syndrome.

Conclusion

The study concludes that albuminuria and impaired renal microcirculation, reflected by high renal Doppler indices, significantly impact myocardial function in nephrotic syndrome. Elevated ACR might correlate with subtle GLS changes indicating subclinical cardiac dysfunction even in patients without overt cardiac symptoms. Speckle tracking echocardiography and renal Doppler ultrasonography are effective, non-invasive tools for early detection of cardiac abnormalities and assessing cardiovascular risk in these patients

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