Echocardiographic Changes in Prevalent Hemodialysis Population Based on Cardiac Symptomatology

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Abstract

Background Despite the prevalence of cardiovascular complications in hemodialysis (HD) patients, routine screening for asymptomatic individuals remains underexplored in clinical practice, particularly beyond those assessed for kidney transplantation. This study aimed to investigate echocardiographic changes in prevalent HD patients, irrespective of symptomatic presentation.

Subjects and Methods A prospective, single-center study spanning 36 months included 79 HD patients. Grouping was based on cardiac symptomatology assessed with the New York Heart Association (NYHA) classification: group 1 comprised 18 asymptomatic patients (NYHA class I), while group 2 included 61 patients with moderate cardiac symptoms (NYHA classes II and III). Routine laboratory analyses, miRNA 133, hydration, and nutritional parameters were assessed, with echocardiography performed a day post-HD.

Results Demographic data, HD quality, blood pressure, therapy, and most echocardiographic indicators showed no significant differences. Asymptomatic patients exhibited noteworthy cardiac structural and functional abnormalities: 55.5% had left ventricular hypertrophy (LVH), and 72.2% had increased left atrial volume index (LAVi). Concentric hypertrophy was observed in 7/18 asymptomatic patients, while 15/61 symptomatic patients demonstrated concentric left ventricle remodeling. In comparison to group 2, group 1 displayed higher hemoglobin, uric acid, and miRNA 133 concentrations, along with better hydration control and higher lean tissue index.

Conclusion This study advocates for routine echocardiographic and cardiac examinations for all HD patients from the treatment's onset, irrespective of symptoms. Additionally, maintaining optimal volume, nutrition, urate concentrations, and hemoglobin is crucial for comprehensive cardiac care in this population.

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Introduction

Cardiovascular diseases (CVD) constitute a significant burden in the dialysis population, where patients already face complex challenges related to renal dysfunction and hemodialysis (HD) treatment [1]. Despite the elevated incidence of CV complications, routine screening for asymptomatic patients remains largely overlooked in clinical practice. Presently, comprehensive cardiovascular assessment is primarily reserved for those being evaluated for kidney transplantation. However, the potential of identifying early cardiac abnormalities in asymptomatic patients undergoing HD holds promise for timely interventions and improved patient outcomes.

Heart failure (HF) stands as a prominent concern within the dialysis population, often linked to cardiac remodeling and the hemodynamic stresses associated with renal dysfunction [2]. Typical symptoms like dyspnea, fatigue, and edema may overlap with fluid retention and renal anemia, complicating diagnosis. Asymptomatic structural or functional cardiac abnormalities are common before clinical symptoms emerge, highlighting the need for early recognition due to their association with adverse outcomes [3][4]. Also, prediction of the risk of CVD by non-invasive tests used in the general population is limited in dialysis patients [5][6]. Existing non-invasive tests for CVD prediction have limitations in dialysis patients due to poor exercise tolerance and pre-existing electrocardiogram changes. Similarly, biomarker values indicative of HF in the general population should be interpreted cautiously in patients with stage 4 and 5 CKD and those treated with dialysis. Namely, the concentration of BNP and NT-proBNP in the serum can be increased even in the absence of clinically manifested HF for several reasons [7]. The most commonly used system to characterize the severity of HF symptoms is the New York Heart Association (NYHA) functional classification, which is based on a dyspnea grading relative to the intensity of physical activity [8]. However, its efficacy in predicting cardiac abnormalities in prevalent HD patients remains uncertain.

To address these gaps, we conducted a study aimed at investigating echocardiographic changes in prevalent HD patients, irrespective of symptomatic presentation. By examining echocardiographic parameters, this study endeavors to

shed light on the prevalence of cardiac abnormalities in asymptomatic patients and the potential role of echocardiography in early detection.

Method

Patients

This prospective observational study included 79 prevalent hemodialysis (HD) patients treated at the Special Hospital for Internal Diseases, Lazarevac, Serbia. These patients were selected from a larger group of previously analyzed HD patients [9] according to the same criteria: 1. patients older than 18 who spent more than six months on HD; 2. asymptomatic for chest pain or acute coronary syndrome in the past three months; and specific to the current study, 3. no history of coronary artery disease defined as prior acute myocardial infarction or revascularization (through angioplasty or coronary artery bypass) or peripheral vascular disease. The exclusion criterion was the inability of the patients to provide informed consent. Each patient was examined and questioned for signs and/ or symptoms, including edema of the lower extremities, (exertional) dyspnea graded by the New York Heart Association criteria (NYHA I-IV), and paroxysmal nocturnal dyspnea/orthopnea [8], by one independent cardiologist or nephrologist. Based on their cardiac symptomatology, patients were divided into two groups: group 1, without symptoms of cardiac origin (NYHA class I), consisting of 18 patients, and group 2, with moderate symptoms of cardiac origin (NYHA classes II and III), consisting of 61 patients.

The participants were monitored from January 2020 to the end of April 2023. The local Ethics Committee approved the study (number 110/21.1.2020), and written informed consent was obtained from all the participants.

All the measured parameters, i.e., demographic data, laboratory data, and transthoracic echocardiography characteristics, are described in detail in our previous work [9].

1. Demographic data: age, gender, renal disease, comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, malignancy, dyslipidemia), and body mass index (BMI).
2. Dialytic data: duration of dialysis session (four hours three times a week), vintage, dialysis membrane (low and high flow polysulfone membrane), single pool Kt/V [7], interdialytic weight gain, dialysis access, and systolic and diastolic blood pressure before HD session, volume status checked by bioimpedance spectroscopy, using the device Body Composition Monitor (BCM) manufactured by Fresenius Medical Care. The measured volume parameters were: total body water (TBW), extracellular water (ECW), intracellular water (ICW), and fluid overload (OH). OH/ECW >15% indicates overhydration. Body composition parameters included the lean tissue index (LTI, kg/m^2) and fat tissue index (FTI, kg/m^2). LTI, normalized for age, gender, and height, helped assess nutritional status, and LTI < 10% signals malnutrition, while LTI ≥10% denotes normal nutrition [10].
3. Laboratory data: urea, creatinine, uric acid, markers of anemia, lipid fraction, biomarkers of mineral bone disorder were determined by routine laboratory analyses at the respective dialysis session. The level of microRNA-133a was

measured by quantitative real-time PCR (qRTPCR) using the TaqMan advanced miRNA assays (hsa-miR-133a-3p, Catalog number: A25576, hsa-miR-222-3p, Catalog number: A25576; Thermo Fisher Scientific, Waltham, MA). qPCR was done on a Line gene K fluorescence quantitative PCR detection system (BIOER Technology Co, Hangzhou, China). All analyses were performed in triplicate. Based on a literature review, -miR-222-3p was used for normalization as an internal control. Threshold cycle (Ct) values were used to perform normalization, and Ct difference (dCt) values were calculated.

4. Transthoracic echocardiography. To avoid the effect of volume load, all echocardiographic data were collected on the day after HD [11]. Left atrial diameter (LAD), left ventricular (LV) internal diameter at end-diastole (LVIDD), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), right atrial diameter (length and transverse diameter), and right ventricular (RV) diameter (basal and midlevel) were recorded. Considering RV structure, Tricuspid Annular Plane Systolic Excursion (TAPSE), right ventricular systolic pressure (RVSP or SPDK), and tricuspid regurgitation were assessed by 4-ventricular RV dimensions [12][13]. We used chamber LVPWT and IVST to calculate the LV mass. LVM, index of LVM (iLVM), and relative wall thickness-RWT were calculated on-line and categorized according to the recommendations [12]. Based on LVMi, LVH is defined for women > 95 g/m^2 and for men > 115 g/m^2 [12]. RWT allows further classification of iLVM as either concentric hypertrophy (RWT > 0.42) or eccentric hypertrophy (RWT ≤ 0.42). LV ejection fraction (EF) is determined using the modified Simpson method, and diastolic function is assessed by the E/e' ratio, with LV diastolic dysfunction criteria defined: E/e' ≥14, e' <10, LAVi >34 [14]. All echocardiographic measurements were performed by experienced echocardiographic cardiologists who were blinded to the clinical conditions, and intra-observer variability was 4%.

Outcomes

Patients were followed longitudinally for 36 months to monitor clinical outcomes and adverse events. The main outcome of this study was all-cause and cardiovascular mortality. The date and cause of death were recorded from the patients' medical files. Sudden cardiac death, heart failure, myocardial infarction, severe aortic stenosis, aortic dissection, ischemic stroke, and peripheral vascular ischemia were considered causes of cardiovascular death. Infection-related mortality included COVID-19 cases and sepsis. Also, the number and causes of hospitalizations were recorded from the patients' medical records.

Statistical analyses were performed using the SPSS software (version 25.0) and R software (version 3.6.1). Continuous variates with normal distribution were presented as mean ± SD and compared using the Analysis of Variance (ANOVA's) F-ratio statistic. Variables without normal distribution were presented as median with interquartile ranges and compared using the Mann-Whitney U test. Categorical data were presented as the number of cases and percentages and compared using the $\chi 2$ test. Survival curves (Kaplan-Meier) and log-rank test were used to estimate the NYHA class influence on all-cause mortality. Statistical significance was set at $P < 0.05$.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Results

Baseline characteristics

The baseline data on studied patients are presented in Table 1. Out of 79 examined patients, 18 patients had no cardiac symptoms, and 61 patients had mild to moderate cardiac symptoms. No difference in age, gender, comorbidities, dialysis vintage, pre-dialysis blood pressure, treatment, or cardiac rhythm on ECG was found out.

Table 1. Demographic data, hemodialysis vintage, comorbidities, treatment, pre-dialysis blood pressure

	Group 1 (NYHA I) N= 18 pts	**Group 2 (NYHA II+III) N= 61 pts**	**F**	**p**
Age, years,	65.44±3.36	66.90±1.39	0.219	0.641
Sex, m/ f, number	11/7	39/22	0.047	0.830
Underlying kidney disease, number				
DN/Nscl	2/8	13/22	0.927/0.406	0.34/0.53
BEN/GN	3/1	5/4	1.083/0.023	0.31/0.88
PKD/other	-/4	6/11	1.914/0.155	0.17/0.69
HD vintage, months	39.5 (22.25-83.0) 56.22±13.1	46 (20.0-84.5) 61.05±7.2	0.104	0.75
kT/V	1.19±0.05 1.13 (0.99-1.33)	1.12±0.04 1.1 (0.94-1.29)	0.985	0.32
Weight gain, kg	2.99±0.25 2.95 (2.35-3.75)	2.95±0.15 2.8 (2.2-3.6)	0.019	0.89
Smoking, yes	2 (11%)	16 (26.2%)	1.801	0.18
Co-morbidities, number:				
Hypertension	8 (44%)	30 (49.2%)	0.122	0.73

Anemia	16 (88.8%)	53 (86.8%)	0.049	0.82
Treatment, number:				
ACE/ ARB	9/2	32/5	0.033/0.143	0.86/0.71
Beta Blockers/CCB	12/10	38/33	0.112/0.012	0.74/0.91
Statins	1	12	2.015	0.16
Systolic BP, mmHg				
Pre-HD	142.94±5.3	149.67±2.8	1.310	0.256
Diastolic BP, mmHg				
Pre-HD	72.72± 2.4	77.04±1.9	1.181	0.281
ECG, number:				
AV block, yes	2	4	0.295	0.589
RBBB, yes	2	4		

X± SE, M (IQR)

HD- hemodialysis, DN- diabetic nephropathy, Nscl- nephroangiosclerosis, BEN- Balkan Endemic Nephropathy, GN- chronic glomerulonephritis, PDK- polycystic kidney disease, BMI- body mass index, ACE- angiotensin converting enzyme inhibitor, ARB- Angiotensin receptor blockers, CCB- calcium channel blockers, HD- hemodialysis, BP- blood pressure, ECG- electrocardiogram, AV block- atrioventricular block, RBBB- Right Bundle Branch Block

Laboratory analyzes and echocardiographic parameters at baseline

Laboratory analyzes and volume status are presented in Table 2.

Table 2. Laboratory analyzes

	Group 1 NYHA I	Group 2 NYHA II±III	F	p
S-Urea, mmol/l	23.37±1.34	21.06±0.77	2.237	0.139
s-Creatinine, µmol/l	890.87±43.72	813.05±25.01	2.387	0.127
S Urate, µmol/l > 400[1]	396.39±19.38 9/18	350.0±11.08 13/61	4.316	**0.041** **0.033**
Hemoglobin, g/l <100[1] >120[1]	117.17±4. 73 4/18 9/18	100.83±2.53 23/61 8/61	10.449	**0.002** 0.567 **0.002**
Ferritin, ng/ml	416.44±24.35	389.46±13.93	0.925	0.447
Iron, µmol/l	15.72±0.88	13.01±2.5	3.301	0.07
CRP	5.35±6.21	12.81±3.59	1.082	0.302
miRNA	11.71±2.52	3.57±1.53	7.627	**0.009**
Bioimpedance				
OH	1.2 (1.02-2.8) 1.96±0.56	2.85 (1.5-4.6) 3.23±0.32	3.957	**0.050**
ECW	7.85 (4.8-15.6) 9.44±2.56	16.8 (8.8-24.3) 16.86±1.48	5.631	**0.020**
OH/ECW > 15%[1]	7.9 (4.8-15.6) 9.94±2.52 33.3%	17.1 (10.8-24.2) 17.01±1.44 51%	5.938	**0.017** 0.190
ECW/ ICW	0.96 (0.9-1.1) 1.01±0.04	1.1 (1.0-1.2) 1.1±0.02	4.188	**0.044**
LTI	11.9 (10.3-14.5) 13.27±0.82	10.8 (9.3-12.9) 11.28±0.46	4.479	**0.039**

[1]Patient number (comparison by χ^2 test), X± SE, M (IQR)

OH –overhydration, ECW- extracellular water, ICW- intracellular water, LTI index – lean tissue index

The significantly higher serum concentration of Hb, urate, and miRNA 133 was observed in the asymptomatic group of patients. Also, the mean value of OH, ECW, OH/ECW (reflecting hyperhydration), ECW/ICW, and LTI (reflecting fluid overload and malnutrition, indicators of muscle wasting) was significantly higher, while LTI was significantly lower in symptomatic patients. However, the OH/ECW value > 15% had an equal number of patients in both groups. No difference was found in other laboratory analyses.

Table 3 shows the baseline echocardiographic parameters of patients across two groups. More patients in the asymptomatic group 1 had HFpEF, and more patients in the symptomatic group 2 had no signs of HF, but the frequency was similar in both groups. Among patients with HFpEF, diastolic dysfunction was found in three asymptomatic patients from group 1 and 10 symptomatic patients from group 2, and the difference is not significant. The ejection fraction, diameters of heart ventricles and atria, and wall thickness were equal in both groups of patients. About 55.5% of patients from group 1 and 59% in group 2 had LVMi above the upper normal limit, and 72.2% of asymptomatic and 70.5% of symptomatic patients had LAVi above the upper normal limit. Considering left ventricular geometry, 7/18 asymptomatic patients had concentric hypertrophy, and 15 symptomatic patients, but none asymptomatic, had concentric remodeling of the left ventricle.

Table 3. Baseline echocardiographic parameters

	Group 1 **NYHA I**	**Group 2** **NYHA II+III**	**F**	**p**
Heart failure (HF) type: HFrEF HFpEF No HF	 4 (22.2%) 11 (61,1%) 3 (16.7%)	 15 (24.6%) 21 (34.4%) 25 (41%)	0.138	0.289
EF, %	56.83±2.24	56.26±1.14	0.057	0.813
EDD, cm	5.38± 0.14	5.31±0.09	0.158	0.692
ESD, cm	3.62±0.14	3.60±0.09	0.012	0.913
IVs thickness, cm	1.04±0.04	1.11±0.03	1.392	0.242
LV posterior wall, cm	1.05 (0.87-1.2) 1.03±0.04	1.1 (1.0-1.2) 1.08±0.02	1.668	0.200
LVMi, g/m^2	113 (92.5-163.5) 120.38±9.32	119 (92.5-150.5) 123.64±4.5	0.114	0.737
>95 (f)/115(m),[1]	10/18	36/61		1.000

Right ventricle	2.4 (2.2-2.4) 2.32±0.03	2.3 (2.2-2.5) 2.38±0.05	0.427	0.515
RVSP > 35 mmHg[1],	3/18	7/61		0.560
Left atrial, cm >4, [1]	4.05±0.12 9/18	4.01±0.06 35/61	0.078	0.781 0.579
LAVi ml/m^2	44.4 (32.2-56.0) 45.25±3.66	45.0 (32.0-61.3) 48.31±3.12	0.257	0.614
>34 [1]	13/18	43/61		0.887
E/A index	0.87±0.08	0.74±0.04	2.309	0.133
e', cm/s	8.13±0.75	7.55±0.41	1.866	0.176
E/e',[1] <8 8-14 >14	 10 5 3	 27 23 11		0.876
Aortic valve flow velocity, m/s	1.35 (1.17-1.42) 1.43±0.08	1.5 (1.4-1.6) 1.63±0.07	1.860	0.177
Pulmonary valve flow velocity, m/s	1.0 (1.0-1.12) 1.06±0.03	1.1 (1.0-1.2) 1.14±0.02	2.855	0.095
Tricuspid valve flow, m/s	0.7 (0.6-0.7) 0.66±0.01	0.7 (0.6-0.7) 0.67±0.02	0.113	0.738
Left ventricular geometry[1]:				
Normal geometry	6 (33.3%)	16 (26.2%)	0.017	0.561
Concentric hypertrophy	7 (38.9%)	8 (13.1%)		**0.034**
Concentric remodeling	0	15 (24.6%)		**0.017**
Eccentric hypertrophy	5 (27.8%)	22 (36.1%)	0.193	0.662

[1]Patients number (comparison by χ^2 test), X± SE, M (IQR)

EF- ejection fraction. EDD-left ventricular end diastolic diameter. ESD-left ventricular end systolic diameter. IVs-interventricular septum, LAVi-left atrial volume index. LVMi-left ventricular mass index. RVSP- right ventricle systolic pressure, E-early mitral valve flow velocity. A-late mitral valve flow velocity. E/A-ratio of early to late mitral valve flow velocity. e'- early diastolic wave. E/e'-ratio of early mitral valve flow velocity to early Tissue Doppler lengthening velocity, f-

female, m- male.

Longitudinal Monitoring and Outcomes

Outcomes were monitored during the period of 36 months. No difference was found in the frequency and cause of hospitalizations between groups (Table 4).

Table 4. Frequency and causes of death and hospitalizations in the studied asymptomatic and symptomatic hemodialysis patients

	NYHA 1	NYHA 2+3	F	p
Death*,	8 (44.4%)	29 (47.5%)	0.052	0.820
Causes of death:				
Infections	7	21	0.396	0.531
CVD	1	7	0.017	0.896
others	-	1		
Hospitalization, *				
0	8	24	1.803	0.183
1	8	20		
2	2	10		
≥3		7		
Causes				
Infections	7	22	0.491	0.486
CVD	2	11		
others	1	4		

* *patients number*

The most frequent cause of hospitalization was infection, mostly COVID-19, across both groups (29 vs 13, p= 0.006), but the prevalence of infection and CVD as the causes of hospitalization in the groups was equal. Throughout the 36 months of follow-up, 8 patients from group 1 and 29 patients from group 2 died. The causes of death are presented in Table 4. Compared to CVD, the more common cause of death was infection, mainly due to COVID-19 in the groups separately (χ^2 p< 0.04), and across both groups (χ^2 p=0.0002). There was no difference in patients' survival curves among the studied groups, as shown by Kaplan-Meier analysis (data not shown). The medians for survival time—representing the point at

which half the patients were anticipated to remain alive—were as follows: 23 months (IQR 15.2-30.8) for group 1, and 11 months (IQR 7.98-14.01) for group 2, and the difference was not significant (Log Rank, p=0.083).

Discussion

Understanding the cardiac status of asymptomatic patients on HD through echocardiography can aid in early risk stratification and tailored interventions, potentially improving their overall cardiovascular health and outcomes. The main findings of the current study are as follows: 1) asymptomatic patients have significant cardiac structural and functional abnormalities; 2) the potential indicators associated with the differences in NYHA groups are body fluid composition (presumably fluid status indicators) and laboratory findings such as hemoglobin, urate levels, and miRNA 133; and 3) there is no relationship between NYHA groups and long-term all-cause and cardiovascular outcomes in asymptomatic HD patients. No differences in demographic data, HD quality, blood pressure levels, applied therapy, and most echocardiographic indicators suggested that, apart from the NYHA classification, the two studied groups had similar baseline characteristics.

With regard to NYHA functional testing, 22.8% of the prevalent HD patients did not have any cardiac problems. However, they also exhibit substantial cardiac abnormalities. LVH prevalence was insignificantly lower in asymptomatic patients (55.5%) compared to those with symptoms (59%). HFpEF was significantly higher in asymptomatic patients (61%) versus symptomatic patients (34.4%), with a similar frequency of diastolic dysfunction. We noted a frequent occurrence of concentric LVH in asymptomatic patients and concentric remodeling in symptomatic patients. Our findings are in accordance with those of a previous report [15]. LVH is frequent, with its prevalence increasing across CKD stages, culminating in the highest incidence in patients with ESKD [16][17][18]. Similar to the general population, LVH associated with CKD is a complex physiological adaptive response to long-term increases in volume or pressure load, along with other traditional (patient age, hypertension, diabetes mellitus, cigarette smoking, dyslipidemia, obesity), non-traditional (microinflammation and vascular dysfunction, oxidative stress, uremic toxins, and advanced glycation end products), and dialysis-dependent risk factors (anemia, dialysis vintage, interdialytic weight gain, and bone mineral metabolism) [19][20][21][22]. Consequently, changes in myocardial geometry develop. We noticed a significant frequency of concentric LVH in asymptomatic patients from group 1 (which reflects chronic pressure overload) and concentric remodeling in symptomatic patients (reflecting myocardial injury or overload), while eccentric LVH and normal geometry were present in a similar number of patients. Previous studies highlighted the high prevalence of abnormal LV geometry in up to 92% of HD patients, influenced by various factors such as fluid volume, arterial pressure, hemoglobin, bone mineral metabolism, interdialytic weight gain, and dialysis vintage [20][21][22][23][24][25].

Based on the obtained findings that both asymptomatic and symptomatic HD patients exhibit similar changes in myocardial structure and function, it seems plausible that the symptoms marked with NYHA classes II and III in this population may be more attributable to non-cardiac causes rather than solely to cardiac dysfunction. The significant differences in laboratory findings, such as uric acid, hemoglobin, and miRNA 133 levels, and body fluid composition (presumably fluid status indicators) between the two groups might suggest potential indicators associated with the

differences in NYHA classes. All mentioned indicators, except miRNA, are reversible, so their correction is a potential way of improving patients' symptoms.

Although the average values of uric acid were within normal laboratory limits in both groups, their values were found to be significantly higher in asymptomatic patients than in symptomatic patients, and 50% of them had values above the upper laboratory limit. During the past few decades, uric acid itself has been reported to be a risk factor for CVDs in various populations, including the general population with no comorbidities and those with hypertension, congestive HF, and diabetes [26]. Serum uric acid levels have been reported to be associated with structural and functional cardiac diseases, including LVH and LV diastolic dysfunction in patients with progressive CKD [27]. Hypouricemia is associated with LVH, endothelial vascular injury, and higher all-cause and cardiovascular mortalities in HD patients [28][29][30]. However, the underlying mechanisms are unclear and inconsistent. It has been postulated to act as a nutritional or inflammation biomarker [31] and as a contributor to oxidative stress at the myocyte level[32].

In our study, higher hemoglobin levels were found in asymptomatic HD patients, and 75% of them were treated with erythropoietin-stimulating agents (ESA) and/or iron supplementation (data not presented). In contrast, 40% of the patients with moderate cardiac symptoms were treated with ESA and/or iron. It is well known that anemia is an independent risk factor for LV dilation, LV hypertrophy, and death in dialysis patients [33]. The mechanism of the connection between CKD, anemia, and cardiovascular events, known as cardio-renal-anemia syndrome, is complex. Briefly, chronic renal anemia could be causally linked to CVD, with decreased oxygen-carrying capacity and oxygen delivery leading to peripheral tissue hypoxia and cell death, with consequent peripheral vasodilation, increased preload and afterload, stimulation of neurohormonal activity, adverse remodeling, dysrhythmia, increased hypertrophy, and progressive cardiac dysfunction [34]. The hemoglobin increase led to a significant reduction and loss of symptoms accompanying anemia[35], but would also be expected to have cardiovascular benefits. In clinical practice, the results of anemia correction's impact on LVH showed inconsistent results: some smaller, non-randomized studies showed regression of LVH [36][37][38], and others did not show a significant cardiovascular benefit, including LVH regression [39]. As anemia in dialysis patients is associated with reduced exercise tolerance, fatigue, and a generally poorer quality of life, its correction and indicators of iron metabolism are advised according to the guidelines for the treatment of anemia [40].

In comparison to symptomatic patients, higher levels of miRNA 133 were found in asymptomatic patients in the present study. Regardless of the significance of the difference, the study did not show the functional significance of miRNA-133, or their direct relationship with subclinical cardiac abnormalities. By pairing with target mRNAs encoding proteins, miRNAs regulate the expression of these mRNAs at the post-transcriptional level. Several miRNAs participate in various crucial biological processes in the human body. Based on accumulating evidence, miRNAs function as important regulators of cardiovascular disorders [41]. miRNA-133 participates in the proliferation, differentiation, survival, hypertrophic growth, and electrical conduction of cardiac cells, which are essential for cardiac fibrosis, cardiac hypertrophy, and arrhythmia, which are the most important physiological or pathological changes observed in cardiac remodeling and directly affect cardiac function and even cause death [42]. All these raise the importance of miRNA-133 in the context of cardiac health in HD patients, but further research is essential to uncover its functional significance and direct associations with subclinical

cardiac abnormalities.

Fluid overload, assessed by bioimpedance, was common in the dialysis population. Previous studies have shown that sustained overhydration is associated with cardiovascular structural and functional changes and cardiovascular mortality [43][44]. Our results were in line with the aforementioned studies and showed that the patient's complaints, assessed by NYHA class, are related to hyperhydration, being more pronounced in patients with moderate symptoms compared to those who had no symptoms. Bearing in mind a previous study that has shown that long-term volume control reduces mortality and improves the quality of life of HD patients [43], it could be concluded that management of volume balance is an important subject of dialysis treatment. Also, our asymptomatic patients had significantly higher LTI in comparison to symptomatic ones. Both findings (controlled hydration and higher LTI) in our asymptomatic patients agree with previously published data [45]. LTI has recently been reported to be important for assessing the risk of protein-energy wasting, as well as a measure of malnutrition in HD patients [45]. This finding indicates the importance of nutritional control in HD patients.

The lack of significant differences in the number of hospitalizations, survival outcomes, all-cause mortality, and cardiovascular mortality, despite differences in laboratory and fluid composition findings between NYHA groups, might suggest that these factors, as measured at the beginning of the study, might not be strong predictors of mortality within the observed timeframe of 36 months. As the present study was carried out during the COVID-19 pandemic, the dominant cause of death was COVID-19 infection in 75% of the examined patients (equal frequency in both groups), compared to 21% who died due to *de novo* CVD (acute myocardial infarction, cerebrovascular insult). It is well known that COVID-19 infection has caused a substantial increase in mortality rates among the general population and various patient populations, including those with cardiovascular diseases, and patients with chronic kidney disease and on renal replacement therapy, as it was already reported [46]. Our results led us to suspect that COVID-19 infection might have masked the impact of CVD on patients' survival.

Nevertheless, the study provides insights into long-term stability, despite initial differences. However, further investigation into fluid status, laboratory findings, and miRNA levels is crucial. Exploring these biomarkers' relationships with subclinical cardiac abnormalities and their predictive value for outcomes could inform risk stratification and management in HD patients.

Limitations

It is essential to acknowledge the limitations of our study, including the small sample size and the single-center design, which may limit the generalizability of our findings. Relying solely on the NYHA classification may overlook symptoms, and alternative assessment tools or combining clinical assessments with patient-reported outcomes could enhance understanding [47]. Also, echocardiography, while valuable, has limitations, suggesting the exploration of advanced techniques or additional biomarkers for a comprehensive evaluation.

Conclusion

The present study highlights the need for a more comprehensive understanding of cardiac abnormalities in asymptomatic HD patients beyond conventional echocardiographic assessments. It suggests potential alternative indicators such as fluid and nutritional status, hemoglobin, uric acid, and miRNA 133 levels that might be associated with differences in NYHA classification. Further investigation into the non-cardiac factors contributing to symptoms in NYHA classes II and III HD patients could provide valuable insights into optimizing management strategies for symptom control and improving patient outcomes. Additionally, exploring whether interventions targeting these non-cardiac factors could alleviate symptoms and improve quality of life in symptomatic HD patients would be worthwhile.

References

1. ^*Fox CS, Matsushita K, Woodward M, et al; Chronic Kidney Disease Prognosis Consortium (2012). Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 380(9854):1662-73. doi: 10.1016/S0140-6736(12)61350-6. Epub 2012 Sep 24.*
2. ^*Parfrey PS (2000). Cardiac disease in dialysis patients: diagnosis, burden of disease, prognosis, risk factors and management. Nephrol Dial Transplant. 15 Suppl 5:58-68. doi: 10.1093/ndt/15.suppl_5.58. PMID: 11073277.*
3. ^*Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS (2003). Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation. 108(8):977-82. doi: 10.1161/01.CIR.0000085166.44904.79. Epub 2003 Aug 11. PMID: 12912813.*
4. ^*SOLVD Investigators; Yusuf S, Pitt B, Davis CE, Hood WB Jr, Cohn JN (1992). Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 327(10):685-91. doi: 10.1056/NEJM199209033271003. Erratum in: N Engl J Med 1992 Dec 10;327(24):1768. PMID: 1463530.*
5. ^*Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, Sarnak MJ. (2007) The Framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol. 50(3):217-24. doi: 10.1016/j.jacc.2007.03.037. Epub 2007 Jul 2. PMID: 17631213.*
6. ^*De Vriese AS, Vandecasteele SJ, Van den Bergh B, De Geeter FW (2012) Should we screen for coronary artery disease in asymptomatic chronic dialysis patients? Kidney Int. 81(2):143-51. doi: 10.1038/ki.2011.340. Epub 2011 Sep 28. PMID: 21956188.*
7. a, b*Wang AY, Lai KN (2008). Use of cardiac biomarkers in end-stage renal disease. J Am Soc Nephrol. 19(9):1643-52. doi: 10.1681/ASN.2008010012. Epub 2008 Mar 5. PMID: 18322158.*
8. a, b*The Criteria Committee of the New York Heart Association. Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis. 6th edition. Boston, MA: Little Brown, 1964*
9. a, b*Dobričić M, Pakić V, Arsenović A, Pejović V, Kuzmanović A, Milić M, Ležaić V. Chronic heart failure phenotypes in prevalent patients treated with hemodialysis – a single-center experience. Srp Arh Celok Lek. 2022;150(11-12):662-668, DOI: https://doi.org/10.2298/SARH220509096D*

10. ^Chamney PW, Wabel P, Moissl UM, Müller MJ, Bosy-Westphal A, Korth O, Fuller NJ (2007). A whole-body model to distinguish excess fluid from the hydration of major body tissues. Am J Clin Nutr. 85(1):80-9. doi: 10.1093/ajcn/85.1.80. PMID: 17209181.
11. ^Zoccali C (2011). Left ventricular mass index as an outcome measure in clinical trials in dialysis patients: a word of caution. Am J Nephrol. 33(4):370-2. doi: 10.1159/000326239. Epub 2011 Mar 30. PMID: 21447944.
12. a, b, cDevereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N (1986). Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol. 57(6):450-8. doi: 10.1016/0002-9149(86)90771-x. PMID: 2936235.
13. ^Lang RM, Badano LP, Mor-Avi V, et al (2015). Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003. PMID: 25559473
14. ^Nagueh SF, Smiseth OA, Appleton CP, et al (2016). Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29(4):277–314
15. ^Malik J, Kudlicka J, Valerianova A, Kovarova L, Kmentova T, Lachmanova J (2019). Diastolic dysfunction in asymptomatic hemodialysis patients in the light of the current echocardiographic guidelines. Int J Cardiovasc Imaging. 35(2):313-317. doi: 10.1007/s10554-019-01564-2. Epub 2019 Feb 27. PMID: 30815807.
16. ^Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE (1995). Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 47(1):186–92. doi: 10.1038/ki.1995.22,
17. ^Eckardt KU, Scherhag A, Macdougall IC, et al (2009). Left ventricular geometry predicts cardiovascular outcomes associated with anemia correction in CKD. J Am Soc Nephrol.20(12):2651-60. doi: 10.1681/ASN.2009060631. Epub 2009 Oct 22. PMID: 19850955; PMCID: PMC2794228.
18. ^Park M, Hsu CY, Li Y, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Group (2012). Associations between kidney function and subclinical cardiac abnormalities in CKD. J Am Soc Nephrol. 23(10):1725-34. doi: 10.1681/ASN.2012020145. Epub 2012 Aug 30. PMID: 22935481; PMCID: PMC3458463.
19. ^Harnett JD, Kent GM, Barre PE, Taylor R, Parfrey PS (1994). Risk factors for the development of left ventricular hypertrophy in a prospectively followed cohort of dialysis patients. J Am Soc Nephrol 4(7):1486–90. doi: 10.1681/asn.v471486,
20. a, bTirmenstajn-Jankovic B, Dimkovic N, Radojicic Z, Bastac D, Zivanovic M, Zikic S (2017). Association between age and cardiovascular status by echosonography in asymptomatic predialysis patients with chronic kidney disease. Saudi J Kidney Dis Transpl.28(4):818-829. PMID: 28748884.
21. a, bEchefu G, Stowe I, Burka S, Basu-Ray I, Kumbala D (2023). Pathophysiological concepts and screening of cardiovascular disease in dialysis patients. Front. Nephrol. 3:1198560. doi: 10.3389/fneph.2023.1198560
22. a, bDimitrijevic Z, Cvetkovic T, Stojanovic M, Paunovic K, Djordjevic V (2009). Prevalence and risk factors of myocardial remodeling in hemodialysis patients. Ren Fail. 31(8):662-7. doi: 10.3109/08860220903100705. PMID: 19817519.
23. ^Wang H, Liu J, Yao XD, Li J, Yang Y, Cao TS, Yang B (2012). Multidirectional myocardial systolic function in

hemodialysis patients with preserved left ventricular ejection fraction and different left ventricular geometry. Nephrol Dial Transplant. 27(12):4422-9. doi: 10.1093/ndt/gfs090. Epub 2012 May 4. PMID: 22561582.

24. ^*Ito T, Akamatsu K (2023). Echocardiographic manifestations in end-stage renal disease. Heart Fail Rev. doi: 10.1007/s10741-023-10376-5. Epub ahead of print. PMID: 38071738.*
25. ^*Zhao X, Zhu L, Jin W, et al (2022). Echocardiographic left ventricular hypertrophy and geometry in Chinese chronic hemodialysis patients: the prevalence and determinants. BMC Cardiovasc Disord. 22(1):55. doi: 10.1186/s12872-022-02506-y. PMID: 35172749; PMCID: PMC8851800.*
26. ^*Høieggen A, Alderman MH, Kjeldsen SE, et al; LIFE Study Group (2004). The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int. 65(3):1041-9. doi: 10.1111/j.1523-1755.2004.00484.x. PMID: 14871425*
27. ^*Kim IY, Ye BM, Kim MJ, et al (2021). Association between serum uric acid and left ventricular hypertrophy/left ventricular diastolic dysfunction in patients with chronic kidney disease. PLoS One. 16(5):e0251333. doi: 10.1371/journal.pone.0251333. PMID: 33956863; PMCID: PMC8101764.*
28. ^*Selim G, Stojceva-Taneva O, Tozija L, et al (2019). Uric acid and left ventricular hypertrophy: another relationship in hemodialysis patients. Clin Kidney J.14(2):578-585. doi: 10.1093/ckj/sfz172. PMID: 33623682; PMCID: PMC7886584.*
29. ^*Harada M, Fujii K, Yamada Y, Tsukada W, Tsukada M, Hashimoto K, Kamijo Y (2020). Relationship between serum uric acid level and vascular injury markers in hemodialysis patients. Int Urol Nephrol. 52(8):1581-1591. doi: 10.1007/s11255-020-02531-w. Epub 2020 Jun 17. PMID: 32557375.*
30. ^*Wang H, Liu J, Xie D, Liu H, Zhen L, Guo D, Liu X (2021). Elevated serum uric acid and risk of cardiovascular or all-cause mortality in maintenance hemodialysis patients: A meta-analysis. Nutr Metab Cardiovasc Dis.31(2):372-381. doi: 10.1016/j.numecd.2020.11.017. Epub 2020 Nov 25. PMID: 33485730.*
31. ^*Beberashvili I, Erlich A, Azar A, et al (2016). Longitudinal Study of Serum Uric Acid, Nutritional Status, and Mortality in Maintenance Hemodialysis Patients. Clin J Am Soc Nephrol. 11(6):1015-1023. doi: 10.2215/CJN.10400915. Epub 2016 Mar 29. PMID: 27026520; PMCID: PMC4891753.*
32. ^*Chen CC, Hsu YJ, Lee TM (2011). Impact of elevated uric acid on ventricular remodeling in infarcted rats with experimental hyperuricemia. Am J Physiol Heart Circ Physiol. 301(3):H1107-17. doi: 10.1152/ajpheart.01071.2010. Epub 2011 May 27. PMID: 21622823.*
33. ^*Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE (1996). The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. Am J Kidney Dis (1996) 28(1):53–61. doi: 10.1016/s0272-6386(96)90130-4*
34. ^*Silverberg DS, Wexler D, Iaina A (2004). The role of anemia in congestive heart failure and chronic kidney insufficiency: the cardio renal anemia syndrome. Perspect Biol Med. 47(4):575-89. doi: 10.1353/pbm.2004.0072. PMID: 15467179.*
35. ^*Delano BG (1989). Improvements in quality of life following treatment with r-HuEPO in anemic hemodialysis patients. Am J Kidney Dis. 14(2 Suppl 1):14-8. PMID: 2757025.*
36. ^*Lezaić V, Vujisić B, Djukanović L, Simin N, Veljović R (1992). Effect of recombinant human erythropoietin therapy on left ventricular hypertrophy in hemodialysis patients. Clin Nephrol. 38(3):174-6. PMID: 1395176.*

37. ^*Frank H, Heusser K, Höffken B, Huber P, Schmieder RE, Schobel HP (2004). Effect of erythropoietin on cardiovascular prognosis parameters in hemodialysis patients. Kidney Int. 66(2):832-40. doi: 10.1111/j.1523-1755.2004.00810.x. PMID: 15253740.*

38. ^*Hampl H, Hennig L, Rosenberger C, Gogoll L, Riedel E, Scherhag A (2005). Optimized heart failure therapy and complete anemia correction on left-ventricular hypertrophy in nondiabetic and diabetic patients undergoing hemodialysis. Kidney Blood Press Res. 28(5-6):353-62. doi: 10.1159/000090190. Epub 2006 Mar 7. PMID: 16534231*

39. ^*Foley RN, Parfrey PS, Morgan J, et al (2000). Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int. 58(3):1325-35. doi: 10.1046/j.1523-1755.2000.00289.x. PMID: 10972697.*

40. ^*Babitt JL, Eisenga MF, Haase VH, et al; Conference Participants. Controversies in optimal anemia management: conclusions from a Kidney Disease (2021): Improving Global Outcomes (KDIGO) Conference. Kidney Int.99(6):1280-1295. doi: 10.1016/j.kint.2021.03.020. Epub 2021 Apr 8. PMID: 33839163*

41. ^*Wronska A, Kurkowska-Jastrzebska I, Santulli G. (2015). Application of microRNAs in diagnosis and treatment of cardiovascular disease. Acta Physiol (Oxf). 213(1):60-83. doi: 10.1111/apha.12416. Epub 2014 Nov 24. PMID: 25362848.*

42. ^*Li N, Zhou H, Tang Q. (2018). miR-133: A Suppressor of Cardiac Remodeling? Front Pharmacol. 9:903. doi: 10.3389/fphar.2018.00903. PMID: 30174600; PMCID: PMC6107689.*

43. [a, b]*Dekker MJ, Marcelli D, Canaud BJ, et al.; MONDO Initiative (2017). Impact of fluid status and inflammation and their interaction on survival: a study in an international hemodialysis patient cohort. Kidney Int 91(5):1214–23.*

44. ^*van der Sande FM, van de Wal-Visscher ER, Stuard S, Moissl U, Kooman JP. (2020). Using Bioimpedance Spectroscopy to Assess Volume Status in Dialysis Patients. Blood Purif. 49(1-2):178-184. doi: 10.1159/000504079. Epub 2019 Dec 18. PMID: 31851988; PMCID: PMC7114899.*

45. [a, b]*Hwang SD, Lee JH, Lee SW, Kim JK, Kim MJ, Song JH. (2018). Risk of overhydration and low lean tissue index as measured using a body composition monitor in patients on hemodialysis: a systemic review and meta-analysis. Ren Fail. 40(1):51-59. doi: 10.1080/0886022X.2017.1419963. PMID: 29347876; PMCID: PMC6014525*

46. ^*Hilbrands LB, Duivenvoorden R, Vart P, et al; ERACODA Collaborators. (2020). COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant 35:1973-1983. doi: 10.1093/ndt/gfaa261.*

47. ^*Chawla LS, Herzog CA, Costanzo MR, Tumlin J, Kellum JA, McCullough PA, Ronco C; ADQI XI Workgroup (2014). Proposal for a functional classification system of heart failure in patients with end-stage renal disease: proceedings of the acute dialysis quality initiative (ADQI) XI workgroup. J Am Coll Cardiol.63(13):1246-1252. doi: 10.1016/j.jacc.2014.01.020. Epub 2014 Feb 12. PMID: 24530671*