Research Article

Echocardiographic Changes in Prevalent Hemodialysis Population Based on Cardiac Symptomatology

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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 an 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 a higher lean tissue index. All these dependent variables show a statistically significant relation to the NYHA: approximately 13% of the variance in Hb levels and 18% of the variance in miRNA can be explained by NYHA classification.
Conclusion: This study advocates for routine echocardiographic and cardiac examinations for all HD patients from the onset of treatment, irrespective of symptoms. Maintaining optimal volume, nutrition, urate concentrations, and hemoglobin is crucial for comprehensive cardiac care in this population. Additionally, exploring whether interventions targeting these non-cardiac factors could alleviate symptoms and improve the quality of life in symptomatic HD patients would be worthwhile.

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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, the 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 76 HD patients, selected from the group of all 96 patients treated with HD in the Special Hospital for Internal Diseases, Lazarevac, Serbia, analyzed in our previous work [9]. The inclusion criteria were the same as in the mentioned paper, i.e., patients older than 18 years who had spent more than six months on HD; asymptomatic for chest pain or acute coronary syndrome in the last three months. Exclusion criteria were the patients' inability to provide informed consent and a positive medical history for the existence of cardiovascular disease defined as previous acute myocardial infarction or revascularization (through angioplasty or coronary artery bypass grafting) or peripheral vascular disease.

Each patient was examined and questioned for signs and/or symptoms, including lower extremities edema, (exertional) dyspnea graded by the New York Heart Association criteria (NYHA I–IV), and paroxysmal nocturnal dyspnea/orthopnea [8] by one well-trained and 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. According to the recommendations of the National Kidney Foundation Quality of Outcomes for Kidney Disease guidelines from 2004, hypertension in patients treated with hemodialysis is defined when blood pressure is >140/90 mmHg before hemodialysis [10]. 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 [11].
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 7500 Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). 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 [12]. 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 [13] [14]. 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 [13]. Based on LVMi, LVH is defined for women > 95 g/m^2 and for men > 115 g/m^2 [13]. 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 [15]. 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 variables with a normal distribution were presented as mean ± SD and compared using the Analysis of Variance (ANOVA) F-ratio statistic. Variables without a 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 χ2 test. Survival curves (Kaplan-Meier) and the 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. Normal pre-HD systolic BP was found in 50% of patients in group 1 and 31% in group 2, while normal diastolic BP was found in 94.4% in group 1 and 85% in group 2 of patients (data not presented in Table 1, p=0.167).

	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 BEN/GN PKD/other	2/8 3/1 –/4	13/22 5/4 6/11	0.927/0.406 1.083/0.023 1.914/0.155	0.34/0.53 0.31/0.88 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 Anemia	8 (44%) 16 (88.8%)	30 (49.2%) 53 (86.8%)	0.122 0.049	0.73 0.82
Treatment, number: ACE/ ARB Beta Blockers/CCB Statins	9/2 12/10 1	32/5 38/33 12	0.033/0.143 0.112/0.012 2.015	0.86/0.71 0.74/0.91 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 RBBB, yes	2 2	4 4	0.295	0.589

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

X± SE, M (IQR)

f– female, m– male, HD– hemodialysis, DN– diabetic nephropathy, Nscl–nephroangiosclerosis, BEN– Balkan Endemic Nephropathy, GN– chronic glomerulonephritis, PKD– polycystic kidney disease, ACE– angiotensin converting enzyme inhibitor, ARB– Angiotensin receptor blockers, CCB– calcium channel blockers, 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.

	Group 1 NYHA I	Group 2 NYHA II±III	F	p	η^2 (adjusted η^2)
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	0.057 (0.044)
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	0.130 (0.117)
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, mg/dl	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	0.179 (0.155)
Bioimpedance					
OH, l	1.2 (1.02–2.8) 1.96±0.56	2.85 (1.5–4.6) 3.23±0.32	3.957	0.050	0.052 (0.039)
ECW, l	7.85 (4.8–15.6) 9.44±2.56	16.8 (8.8–24.3) 16.86±1.48	5.631	0.020	0.074 (0.061)
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	0.077 (0.064)
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	0.055 (0.042)
LTI index, kg/m^2	11.9 (10.3–14.5) 13.27±0.82	10.8 (9.3–12.9) 11.28±0.46	4.479	0.039	0.059 (0.046)

Table 2. Laboratory analyses

The significantly higher mean values of serum concentration of Hb, urate, miRNA 133, OH, ECW, OH/ECW (reflecting hyperhydration), ECW/ICW, and LTI (reflecting fluid overload and malnutrition, an indicator of muscle wasting) were observed in the asymptomatic group of patients, while LTI was significantly lower in symptomatic patients. All these dependent variables show a statistically significant relation to the NYHA, but with different effect sizes- η^2 (Table 2). Hb and miRNA show larger effect sizes, and approximately 13% of the variance in Hb levels and 18% of the variance in miRNA can be explained by NYHA classification. 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. At the same time, by examining the ECG records, indicators of LVH were found in 3 patients of group 1 and 9 patients of group 2 (NS). 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.

	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

	Group 1 NYHA I	Group 2 NYHA II+III	F	p
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

Table 3. Baseline echocardiographic parameters

[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

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).

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

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

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 plots among the studied groups, as shown by Kaplan–Meier analysis (Figure 1).
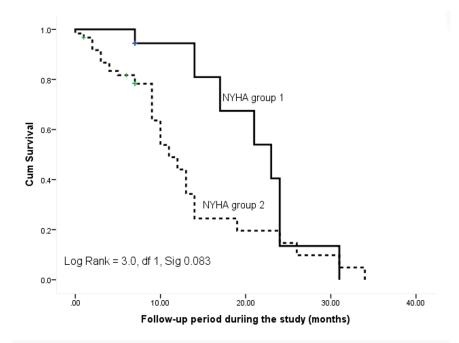
Figure 1. Survival plots for two studied groups (Kaplan–Meier analysis)

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, χ^2 = 3.0, 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 exhibited 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 [16]. LVH is frequent, with its prevalence increasing across CKD stages, culminating in the highest incidence in patients with ESKD [17][18][19]. 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) [20][21][22][23]. 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 [21][22][23][24][25][26].

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 could have more pronounced practical implications.

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 [27]. 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 [28]. Hypouricemia is associated with LVH, endothelial vascular injury, and higher all-cause and cardiovascular mortalities in HD patients [29][30][31]. However, the underlying mechanisms are unclear and inconsistent. It has been postulated to act as a nutritional or inflammation biomarker [32] and as a contributor to oxidative stress at the myocyte level [33].

In our study, a significant relationship between the NYHA group and Hb levels was found. Higher Hb 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 [34]. 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 [35]. The hemoglobin increase led to a significant reduction and loss of symptoms accompanying anemia [36], 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 [37][38][39], and others did not show a significant cardiovascular benefit, including LVH regression [40]. 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 [41].

A strong relationship between the NYHA group and specific miRNA-133 might indicate that miRNA-133 could serve as a biomarker for heart failure severity or as a potential therapeutic target. 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 [42]. 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 [43]. 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 [44][45]. Our results were in line with the aforementioned studies and show 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 [44], it could be concluded that the management of volume balance is an important subject of dialysis treatment. Also, our asymptomatic patients had a significantly higher LTI in comparison to symptomatic ones. Both findings (controlled hydration and higher LTI) in our asymptomatic patients agree with previously published data [46]. 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 [47]. 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 was already reported [48]. Our results led us to suspect that COVID-19 infection might have masked the impact of CVD on patients' survival. Investigations of the cardiovascular profile of these HD patients after the pandemic and interventional investigations for the prevention of cardiovascular diseases will be of particular interest.

Our study highlights the long-term stability of HD patients, despite initial symptom variations due to non-cardiac causes. Monitoring fluid status, Hb levels, uric acid, and miRNA-133 is crucial before assessing cardiovascular status. Investigating the relationships between these biomarkers, non-invasive cardiac assessments, subclinical cardiac abnormalities, and their predictive value for outcomes can enhance 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, Hb, 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 the quality of life in symptomatic HD patients would be worthwhile.

Statements and Declarations

Visualization, VL.; Supervision, VL.; All authors have read and approved the final article.

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Declarations

Potential competing interests: No potential competing interests to declare.