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Comparison of lung ultrasonography, transthoracic echocardiography and clinical findings in assessing volume status in patients receiving renal replacement therapy

Gizem Basturk[1], Serkan Bakirdogen[2], Ugur Kucuk[3], Nilufer Aylanc[4], Zubeyir Celik[1], Gokhan Basturk[5]

[1]*Çanakkale Onsekiz Mart University School of Medicine Department of Internal Medicine, Çanakkale, Türkiye*
[2]*Çanakkale Onsekiz Mart University School of Medicine Department of Internal Medicine Division of Nephrology, Çanakkale, Türkiye*
[3]*Çanakkale Onsekiz Mart University School of Medicine Department of Cardiology, Çanakkale, Türkiye*
[4]*Çanakkale Onsekiz Mart University School of Medicine Department of Radiology, Çanakkale, Türkiye*
[5]*Çanakkale Provincial Health Directorate, Çanakkale, Türkiye*

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Abstract

While transthoracic echocardiography and clinical findings are used to assess body volume status, lung ultrasonography (LUS), which is a non-invasive method, has also been used in assessing hypervolemia in recent years. This study aims to compare LUS, transthoracic echocardiography (TTE) and clinical findings in the assessment of body volume status in patients receiving renal replacement therapy (RRT). The study included 99 subjects who received RRT and were followed-up in our hospital. The patients were randomly selected from kidney transplant patients and those who had been receiving peritoneal dialysis (PD) or hemodialysis (HD) for at least the past three months. In addition, a control group consisting of 52 healthy subjects was also enrolled. LUS and TTE were simultaneously performed (within 24 hours). The mean left atrial (LA) diameter was 37.8±2.7 mm, 37.9±3.4 mm, 38.6±3.5 mm and 29.0±4.4 mm in patients who received PD, kidney transplantation, HD and in the control group, respectively. There was a moderate positive correlation between the total number of B-lines and LA diameter (mm) in the combined group consisting of the patient and control groups ($p=0.0001$, $r=0.286$). In this study, the number of B-lines on LUS has been found to be higher in patients receiving renal replacement therapy due to the effect of hypervolemia compared to the control group. However, there was no statistically significant difference in terms of the number of B-lines and LA diameter in echocardiography.

Keywords: Hypervolemia, renal replacement therapy, lung ultrasonography, transthoracic, echocardiography

Introduction

Various methods such as physical examination, bioimpedance analysis, test for serum natriuretic peptide levels, transthoracic echocardiography and inferior vena cava evaluation are used to determine the body volume status [1]. In recent years, lung ultrasonography (LUS), which is a noninvasive method, has been used in assessing hypervolemia. LUS determines the amount of fluid in extravascular lung tissue (interstitium) and provides information about the volume status of the body based on the number of B-lines. The number of B-lines increases in hypervolemia and decreases after dialysis. In patients undergoing hemodialysis, B-lines are indicators of both hypervolemia and left ventricular dysfunction [2]. This study aims to compare LUS, transthoracic echocardiography (TTE) and clinical findings in the assessment of body volume status in patients receiving renal replacement therapy (RRT).

Material and Methods

Study site: The study was conducted in Çanakkale Onsekiz Mart University Application and Research Hospital. To comply with the principles of ethics, an ethics committee approval numbered 2021-10 and dated 15.12.2021 was obtained from the Clinical Trials Ethics Committee.

Inclusion and exclusion criteria: Ninety-nine patients with end-stage renal disease (ESRD) who were under treatment and follow-up in our hospital were included in the study. The patients

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Corresponding Author: Gizem Basturk, Çanakkale Onsekiz Mart University School of Medicine Department of Internal Medicine, Çanakkale, Türkiye
Email: basturkgizem35@gmail.com

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were randomly selected from kidney transplant patients and those who were receiving peritoneal dialysis and hemodialysis. In addition, a control group consisting of 52 healthy subjects was also enrolled.

Male and female subjects aged 18-80 who were diagnosed with ESRD and received renal replacement therapy for at least three months were included. Presence of dehydration, interstitial lung disease, scleroderma, morbid obesity and subcutaneous emphysema in patients as well as history of lung surgery, acute infection, malignancy and <18 or >80 years of age were identified as the exclusion criteria.

Our study is a prospective study. Serum biomarkers (urea, creatinine, uric acid, albumin, sodium, potassium, calcium, hemogram, parathyroid hormone, 25-hydroxyvitamin D levels, venous blood gases and complete urinalysis) that were tested for routine workup within the last three months and recorded in the hospital's system were retrospectively utilized.

LUS was performed on each patient and subject with the simple method. LUS (Samsung rs80a device, Korea, April 2017) was performed in subjects in supine position. A 3.5 MHz probe was placed in intercostal spaces on the anterior, mid and posterior axillary lines on both hemithoraces. Presence of B-lines was investigated in areas where lung tissue was best visualized. Both hemithoraces were separately evaluated and the findings were noted. B lines; These are laser beam-like, well-defined, hyperechoic lines that extend vertically, starting from the pleural line to the lower border of the lung tissue visible in the image, moving with the sliding movement of the pleura, erasing the A lines. Visualization of at least 3 B-lines between two ribs on the same line was considered a positive finding (Figure 1).

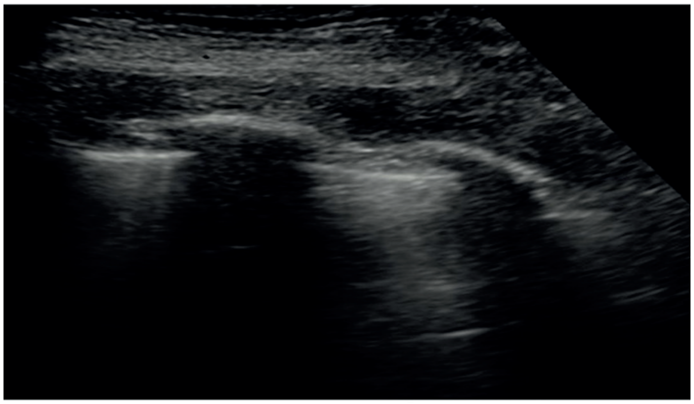

Figure 1. LUS, example of three or more B lines

Transthoracic Echocardiography was performed on all patients with Philips EPIQ 7 device (Philips EPIQ 7 Cardiac Ultrasound, Bothell, WA, USA) using a 2.5 MHz probe. Left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's formula. Echocardiographic evaluations were performed in accordance with the imaging guidelines recommended by the American and European Associations (Figure 2). In transthoracic echocardiography, firstly LA: Left Atrium Diameter, LVEDD: Left Ventricular End Diastolic Diameter, IVS: Interventricular Septum Diameter and RA: Right Atrial Diameter were measured and its correlation with b lines seen in lung ultrasonography was calculated.

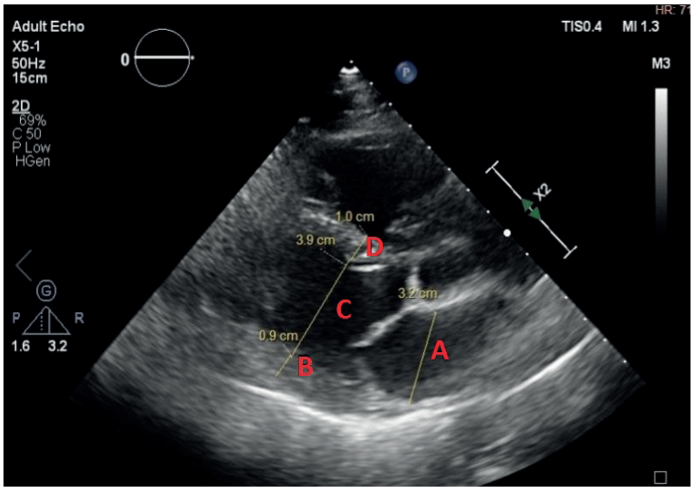

Figure 2. Representations of some measurements in transthoracic echocardiography. (A: Left atrium B: Posterior wall C: End diastolic ventricle diameter D: Interventricular septum)

Statistical Analysis

Data obtained in this study was transferred to SPSS 19.0 in electronic environment. Data check and analysis were performed with the SPSS software. Descriptive statistics were expressed with mean, standard deviation, median, minimum, maximum and percentage values. Significance tests for statistical evaluations involving the comparison of continuous variables were selected based on the result of the normal distribution compliance test. The chi-square significance test was used for discrete variables and the Kruskal-Wallis significance test for continuous variables. Diagnostic value of the left atrial diameter measurement for hypervolemia was evaluated with ROC curve analysis and the curve was drawn. In said analysis, left atrial diameter measurements were compared with TTE findings and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve (AUC) were calculated. $p<0.05$ was considered as statistically significant.

Results

Of the 151 subjects included, 99 were on RRT (peritoneal dialysis, hemodialysis and kidney transplant) and there was a statistically significant difference between the groups in terms of age. Table 1 shows the age distribution by groups (p=0.0001).

Table 1. Distribution of the age status of the subjects according to the groups

	Mean±SD	Median (Min-Max)
Peritoneal dialysis	61.2±13.6	65.5 (38-82)
Kidney transplant	51.4±13.8	54.0 (24-81)
Hemodialysis	58.2±15.1	60.0 (21-77)
Control group	47.8±8.7	44.0 (38-71)
p	**0.0001**	

SD: standart deviation, p: Kruskal-Wallis test

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Eighty (53%) subjects were female and 71 (47%) subjects were male. Evaluation of the patients receiving renal replacement therapy in terms of etiology showed that 41% of the patients had HT, 19% had DM, 9% had chronic glomerulonephritis and urologic causes and 4% had polycystic kidney disease. 17% of the patients had an unknown etiology. The mean time after the initiation of renal replacement therapy was 24.1±20.1, 75.8±76.5 and 35.4±37.1 months in patients receiving PD, kidney transplantation and HD, respectively. There was a statistically significant difference between patient subgroups in terms of the duration of renal replacement therapy (p=0.0001).

Transthoracic echocardiography findings and the measurement results are shown in Table 2, wherein there was a statistically significant difference (p=0.0001).

Table 3 below shows the serum biomarkers, hemogram, venous blood gas and complete urinalysis results of the subjects that were obtained retrospectively for routine workup purposes within the last three months. A statistically significant difference has been observed (p=0.0001).

Table 2. Transthoracic echocardiography findings of subjects

	PD		Kidney transplantation		HD		Control group	
	Mean±SD	**Median (Min-Max)**	**Mean±SD**	**Median (Min-Max)**	**Mean±SD**	**Median (Min-Max)**	**Mean±SD**	**Median (Min-Max)**
LVEF	58.0±4.4	57 (50-67)	57.3±5.0	56.5 (45-68)	57.6±5.6	58 (40-66)	60.7±3.9	60 (48-68)
LVEDD (mm)	44.0±2.8	44 (38-49)	44.0±2.5	44.5 (38-48)	43.7±3.0	44 (38-49)	40.5±2.1	40.5 (36-46)
LVESD (mm)	28.3±2.5	28 (25-34)	28.4±2.0	28 (25-35)	29.0±3.5	28 (23-38)	27.9±1.7	28 (22-31)
IVS (mm)	11.5±1.7	12 (8-14)	11.5±1.3	12 (9-14)	12.1±1.3	12 (9-14)	11.0±1.2	10 (8-14)
PW	9.6±1.5	10 (7-12)	9.5±1.2	9 (8-12)	10.0±1.8	10 (7-15)	8.3±1.2	8 (6-12)
LA (mm)	37.8±2.7	38 (30-42)	37.9±3.4	38 (26-48)	38.6±3.5	38 (31-46)	29.0±4.4	28 (21-41)
Ems	75.6±10.2	77 (52-98)	79.2±6.2	78 (67-90)	78.4±6.8	78 (65-91)	81.5±5.1	81 (66-89)
Ams	76.1±18.3	72.5(41-120)	82.4±8.7	82.5 (65-98)	82.0±6.8	85 (66-91)	70.8±6.6	69.5 (58-88)
E/A	1.0±0.3	1.0 (0.5-2)	0.9±0.1	0.9 (0.7-1.3)	0.9±0.0	0.9 (0.8-1.2)	1.1±0.1	1.1 (0.9-1.4)
sPAP (mmHg)	21.1±3.5	21 (15-30)	20.3±2.7	20 (16-27)	21.0±2.3	21 (16-26)	21.6±1.5	21 (19-25)
RV (mm)	28.7±3.4	28 (24-38)	28.1±3.6	28 (19-37)	29.1±3.5	29 (22-38)	21.5±2.3	21 (19-31)
RA (mm)	30.5±3.3	31 (22-35)	30.7±4.1	31 (21-42)	31.7±2.7	32 (24-37)	22.2±3.3	22 (17-33)

SD: standart deviation. p: Kruskal-Wallis test

Table 3. Biochemical analysis of subjects

	PD		Kidney transplantation		HD		Control group	
	Mean±Sd	**Median (Min-Max)**	**Mean±Sd**	**Median (Min-Max)**	**Mean±Sd**	**Median (Min-Max)**	**Mean±Sd**	**Median (Min-Max)**
Hb (g/dl)	10.5±1.3	11.1 (8.0-12.6)	12.6±2.1	12.7 (8-18.4)	11.4±2.3	11.2 (7.4-18.4)	13.1±1.6	13.4 (9.4-16.8)
Leukocyte (x10^3/ul)	7.6±2.1	7.4 (4.8-11.2)	8.2±2.7	8.2 (3.8-16.1)	8.2±5.5	6.7 (3.9-32.1)	7.4±2.0	6.8 (3.8-13.9)
Platelet (x10^3/ul)	276.6±100.0	260 (141-639)	230.5±60.7	234 (106-367)	241.3±93.2	174 (106-478)	260.1±57.9	254 (140-484)
Urea (mg/dl)	101.7±35.5	94 (45-206)	61.14±41.9	44.5 (16-212)	97.6±38.7	96 (24-205)	24.6±9.5	21 (8-69)
Creatinine (mg/dl)	6.9±3.4	6.3 (1.3-15.2)	2.0±1.2	1.6 (0.6-6.2)	6.0±2.5	6.0 (1.7-11.4)	0.6±0.1	0.6 (0.4-1.1)
Albumin (g/dl)	3.5±0.4	3.6 (2.2-4.2)	4.3±0.4	4.4 (2.6-4.8)	3.9±0.8	4.1 (1.8-5.3)	4.2±0.2	4.3 (3.5-4.9)
Calcium (mg/dl)	8.5±0.7	8.5 (7.1-10.3)	9.6±0.7	9.8 (7.7-11)	9.1±0.8	9.1 (7.5-10.6)	9.4±0.4	9.5 (8.1-10.4)
Sodium (mmol/l)	137.2±3.8	137.5 (129-143)	139.0±3.7	139 (130-151)	138.3±3.5	139 (130-144)	140.0±2.5	140 (133-147)
Potassium (mmol/l)	4.5±0.4	4.5 (3.9-5.5)	4.4±0.5	4.4 (3.4-6.3)	5.1±0.7	5.2 (3.8-6.9)	4.3±0.2	4.4 (3.9-5)
PTH (pg/ml)	401.2±219.4	356.5 (61-900)	164.9±120.8	126 (9-479)	361.1±323.0	287 (11-1633)	52.1±17.0	51.5 (22-94)
25-OH-D_3 (ng/ml)	13.3±9.2	9.5 (3-34)	26.3±9.2	25.5 (8-48)	19.3±11.0	23 (3-48)	14.6±7.2	13 (3-32)
Uric acid (mg/dl)	6.1±1.4	6.1 (4.2-10)	6.4±1.6	6.3 (2.6-11.9)	4.9±1.6	4.8 (2.8-8.5)	4.3±1.3	4.1 (1.6-7.3)
Bicarbonate (in blood gas mmol/l)	22.8±4.6	22.3 (15.1-32.7)	23.0±2.6	23.4 (15.1-27.8)	23.4±3.3	23.3 (11.8-29.9)	23.7±2.0	23.6 (15.3-31)
Protein (in routine urine)	1.5±1.1	1.5 (0-4)	0.4±0.6	0 (0-2)	2.1±0.9	2 (1-4)	0.2±0.6	0 (0-3)

SD: standart deviation. p: Kruskal-Wallis test

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Table 4 shows the correlation analysis for B-lines on LUS and TTE measurements, wherein there was a moderate positive correlation between the total scores LUS and LA diameters (mm) (r=0.286, p=0.0001).

ROC analysis of left atrial diameter measurements in TTE of the subjects in our study is shown in Figure 3. According to the ROC curve analysis, 3 or more B-lines (T-SCORE) was considered as a positive finding. This analysis was performed to determine the LA diameter cut-off value for predicting hypervolemia. NPV was 84.02%, PPV was 57.14%, sensitivity was 14.81% and specificity was 97.58% in the patient group with a left atrial diameter of 42.5 mm and above.

Comparison of the mean number of B-lines LUS and LA diameter (mm) in the patient group did not yield a statistically significant result (p=0.318, r=0.101). Comparison of the mean number of B-lines LUS and RA diameter (mm) in the patient group did not yield a statistically significant result (p=0.932, r=0.009).

Table 4. Correlation analysis of B lines and TTE measurements seen in LUS

LVEDD mm							
LA mm	r=0.561 p=0.0001						
TSCORE	r=0.159 p=0.052	r=0.286 p=.0001					
BLINE R	r=0.142 p=0.083	r=0.215 p=0.008	r=0.867 p=0.0001				
BLINE L	r=0.138 p=0.091	r=0.285 p=0.0001	r=0.894 p=0.0001	r=0.552 p=0.0001			
IVS mm	r=0.361 p=0.0001	r=0.550 p=0.0001	r=0.197 p=0.015	r=0.159 p=0.052	r=0.187 p=0.022		
PW	r=0.301 p=0.0001	r=0.463 p=0.0001	r=0.175 p=0.032	r=0.170 p=0.037	r=0.140 p=0.087	r=0.832 p=0.0001	
RA mm	r=0.509 p=0.0001	r=0.733 p=0.0001	r=0.217 p=0.007	r=0.131 p=0.110	r=0.245 p=0.002	r=0.484 p=0.0001	r=0.374 p=0.0001

*: p<0,05, **: p<0,01, ***. Pearson correlation analysis, Correlation coefficient (3 decimal digits are used after the comma for ease of display), LVEDD: left ventricular end diastolic diameter, LA: left atrium diameter, TSCORE: total number of B lines, B LINE R: number of B lines in right hemithorax, B LINE L: number of B lines in left hemithorax, IVS: interventricular septum diameter, PW: left ventricular intermittent (Pulse Wave) Flow Doppler Measurement, RA: right atrium diameter

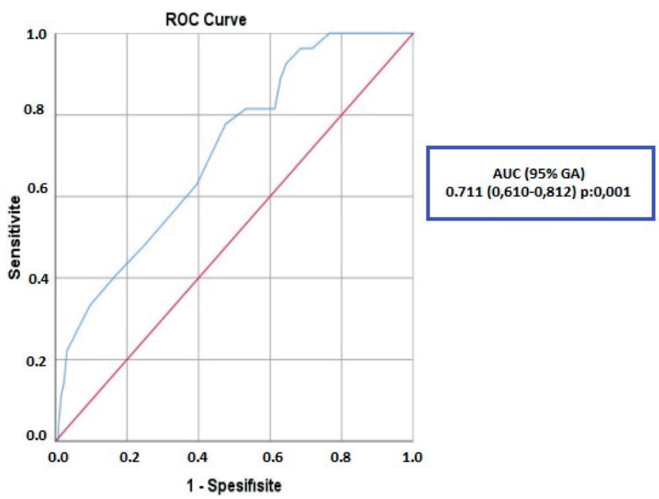

Figure 3. ROC curve analysis of left atrium diameter measurement in TTE of the subjects in our study

Discussion

Majority of patients with end stage renal failure (ESRD) have hypertension due to hypervolemia. Volume burden and increased pressure building up as a result of hypervolemia and hypertension lead to increased myocardial workload, thereby causes left ventricular hypertrophy (LVH) [3]. Patients with LVH who are not diagnosed and treated at an early stage may develop cardiosclerosis and heart failure [4]. This, in turn, leads to increased morbidity and mortality [5].

In 2010, Mallamacı et al. conducted a study demonstrating that hypervolemia assessed by LUS had a strong relationship with cardiac measurements including LVEF and LA diameter in patients receiving HD. However, this study was conducted in accordance with the New York Heart Association (NYHA) classification and bioimpedance analysis performed prior to dialysis [6]. In said study, LUS was performed before and after dialysis in all patients receiving HD. It was found that the number of B-lines increased with age. Patients with NYHA functional class 3 and above (advanced stage) heart failure were mostly observed in the group with number of B-lines >30. Unlike the study by Mallamacı et al., patients receiving RRT consisted of kidney transplant patients and those receiving HD and PD in our study. In addition, a control group was formed with subjects who did not have chronic kidney disease. Patient and control groups were compared in terms of echocardiographic and LUS findings. The study did not include any patients with an ejection fraction below 40% on echocardiography since the subjects included were stable patients who presented to the outpatient clinic. This mainly stemmed from the fact that various factors that patients may exhibit such as low cardiac output, not taking the maximum dose of medications or worsening kidney functions during follow-up would be confounding in the statistical interpretation of the study. In this study, it has been observed that the number of B-lines on LUS (total score) increased with age in both the patient and control groups, respectively ($p=0.034$, $r=0.213$; $p=0.004$, $r=0.234$).

Pardala et al. conducted a study comparing B-lines on LUS with left ventricular function and hydration status in patients receiving hemodialysis. LUS was performed before and after dialysis in all patients. It was found that the number of B-lines on LUS had a positive correlation with left and right atrial volume and size and a negative correlation with LVEF [7]. In our study, when a statistical analysis was performed in all patients receiving RRT (HD, PD and kidney transplant) as well as the control group, moderate positive correlation between B-lines on LUS and left and right atrial diameters ($p=0.0001$, $r=0.286$; $p=0.007$, $r=0.217$) was observed, respectively. Comparison of the mean number of B-lines on LUS with left and right atrial diameters in the patient group did not yield a statistically significant relationship ($p=0.318$, $r=0.101$; $p=0.932$, $r=0.009$), respectively.

In another study, Enia et al. evaluated B-lines on LUS in patients receiving PD. Increased number of B-lines was found to cause physical function loss regardless of the symptomatic or asymptomatic status of the patients. In addition, decreased physical function has been found to be associated with worsening cardiac function [8]. Our study included patients who received HD and kidney transplantation in addition to those receiving PD as the patient group. Physical functioning scale was not used in this study.

In another study conducted by Loutradis et al. in hypertensive and euvolemic patients receiving hemodialysis, it was observed that the treatment (ultrafiltration), managed according to the LUS-guided assessment based on B-lines, was more successful compared to the standard approach based on dry weight. In the study, it was found that inferior vena cava and left atrial diameters were decreased eight weeks after LUS-guided ultrafiltration. Reduction of volume excess in the body with ultrafiltration leads to a decrease in preload which reduces the amount of interstitial fluid in the lungs in heart failure, thereby leading to a lower LUS B-line score [9]. According to our study, there was no statistically significant relationship between total LUS scores and LA diameter in patients receiving RRT. However, the total LUS score and LA diameter were found to have a moderate positive correlation when all subjects including the patient and control groups were evaluated.

One of the most important causes of this situation, which is not in line with the literature, is the fact that the change in LA diameter would be minimal or none as a result of the treatment of patients have developed fibrotic tissue in the left atrium. A cardiac MRI or biopsy is required to definitely assess whether a patient has fibrosis. However, a biopsy or cardiac MRI cannot be performed to detect fibrosis as part of routine practice due to the interventional nature of the former and use of contrast agent in the latter. Although there was a moderate correlation, results of our study have been found to be clinically and statistically significant ($p=0.0001$, $r=0.286$).

One of the important components of cardiac physiology is the left atrium (LA). The heart filling with blood fills the left ventricle in systole and diastole respectively [10]. As a result of the prolonged increase in pressure in the left atrium and the increase in volume load, the left atrium enlarges (LAE) [11]. It most commonly occurs with systemic hypertension, left ventricular hypertrophy and diastolic dysfunction [12]. Current studies have shown the clinical importance of LAE independently in the development of heart failure [13,14]. If patients do not have atrial fibrillation, mitral valve disease, and increased cardiac output, the best indicator of left ventricular dysfunction is enlargement of the left atrium [15]. In our study, left ventricular diastolic dysfunction was increased in subjects with increased left atrium diameter as a result of hypervolemia and there was a clinically and statistically significant correlation between the two ($p=0.0001$, $r=0.561$). In the analysis of LA measurements performed with TTE and total number of B-lines investigated with LUS (T-SCORE), LA diameter cut-off value for predicting hypervolemia has been found to be 42.5 mm. The number of B-lines was increased in patients with an LA diameter measuring 42.5 mm or higher and specificity has been found to be 97.58%.

Our study had some limitations; no matter how high the left atrial diameter is measured in TTE measurement, there may be patients with intact left ventricular function. The catheterization procedure, which is recommended to demonstrate the diameter of the left atrial diameter and left ventricular dysfunction, could not be applied to our patients because it is an invasive procedure. Cardiac MRI, which can also show structural deterioration that may occur due to long-term pressure exposure, could not be performed because it is an invasive procedure that requires contrast material.

Conclusion

In conclusion, in our study, the number of B-lines on LUS was higher in patients receiving renal replacement therapy due to the effect of hypervolemia compared to the control group. In patients receiving renal replacement therapy, lung ultrasound and transthoracic echocardiography should be performed at intervals of 6 months to 1 year. However, there was no statistically significant difference in terms of the number of B-lines and LA diameter in echocardiography. There was a positive correlation between these two markers in the combined group consisting of both the patient and control groups. This could have stemmed from the heterogeneity of the patient group. There is a need for further comparative and prospective studies to be conducted with a higher number of RRT patients.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethics committee approval was obtained from Çanakkale Onsekiz Mart University Clinical Research Ethics Committee with the date 15.12.2021 and number 2021-10.

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