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# Evaluation of alveolar-capillary membrane functions by thoracic ultrasonography in heart failure

Ecem Gürses[1], Mehdi Zoghi[2]

[1]Department of Cardiology, University of Bakırçay School of Medicine, İzmir, Türkiye
[2]Department of Cardiology, Ege University Faculty of Medicine, İzmir, Türkiye

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***ABSTRACT***

**Objectives:** This study aimed to research the effect of the increased B-line count (interstitial fluid accumulation) in patients with congestive heart failure on the diffusion capacity of the alveolar-capillary membrane.

**Patients and methods:** This prospective study was conducted with 77 inpatients diagnosed with pulmonary edema and decompensated heart failure between January 2018 and December 2018. The B-line counts of the patients were calculated through echocardiography and thoracic ultrasonography within the first 24 h of their admission, and the patients were categorized into two groups based on their B-line counts being <15 (n=26; 18 males, 8 females; mean age: 48.6±3.3 years; range, 21 to 72 years) or >15 (n=51; 36 males, 15 females; mean age: 53.7±2.0 years; range, 20 to 79 years). After sufficient diuretic treatment, the patients who were able to tolerate and pass the tests were then subjected to a respiratory function test, diffusion test [DLCO (diffusing capacity of the lungs for carbon monoxide)], and six-minute walk test (6MWT).

**Results:** The following results in study were found in the echocardiography of the patients with a B-line number >15: lower right ventricular ejection fraction (p=0.003), lower right ventricular systolic motion (p=0.014), higher systolic pulmonary artery pressure (p<0.0001), higher tricuspid regurgitant velocity (p=0.001), more dilated vena cava inferior radius (p<0.0001), higher left atrium volume (p=0.007), higher early diastolic transmitral flow velocity/early diastolic mitral anullar velocity (E/e´) >15 (p<0.0001), and higher pleural effusion (p=0.014). The following results were found in the respiratory function test, DLCO test, and 6MWT of the patients with a B-line number >15: lower forced vital capacity (p<0.0001), lower forced expiratory volume in 1 sec (p=0.002), lower corrected DLCO (p<0.0001), lower 6MWT (p<0.0001).

**Conclusion:** B-line counts >15 may be a predictor of a decrease in diffusion capacity, restrictive pattern in respiratory function, decrease in right ventricular function, and increase in pulmonary vascular resistance.

***Keywords:*** Alveolar-capillary membrane, heart failure, thoracic ultrasonography.

Heart failure is a cardiac structural or functional disorder that causes the heart to fail to provide enough oxygen to meet tissues' metabolic needs.[1] Pulmonary edema is the accumulation of fluid in the interstitium and alveoli due to increased pulmonary capillary pressure. Thoracic ultrasonography is one of the methods used in addition to methods such as chest radiography and computed tomography to evaluate this accumulated fluid.[2] B-line pulmonary edema evaluated by thoracic ultrasonography is a portable, nonradiating, and useful noninvasive method.[3-11]

In heart failure, as a result of the development of pulmonary edema, the interstitial tissue of the alveolar-capillary membrane starts to increase; in other words, the extracellular matrix and the thickness of the alveolar-capillary membrane increase due to the increased capillary pressure and the continuous physical stress caused by the increased capillary volume. This situation causes a decrease in gas diffusion.[12-16] The test evaluating alveolar-capillary membrane permeability is the lung diffusion test, which measures the diffusing capacity of the lungs for carbon monoxide (DLCO). The diffusion test is

**Corresponding author:** Ecem Gürses, MD. Bakırçay Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 35665 Menemen, İzmir, Türkiye.
E-mail: eccemm_1988@hotmail.com

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defined as the carbon monoxide uptake rate in mL at 1 min and each mmHg driving pressure, expressed as mL/min/mmHg. An increase in alveolar-capillary membrane thickness and, consequently, decrease in gas diffusion may be one of the predictors of increased mortality in heart failure.

The purpose of our study was to compare the results of B-line count and diffusion test with thoracic ultrasonography in patients with heart failure and to examine the effect of increasing the number of B-lines (interstitial fluid accumulation) on alveolar-capillary membrane diffusion capacity. Furthermore, the study aimed to examine the pulmonary vascular resistance, pulmonary artery pressure, and right ventricular effect due to remodeling in patients with high B-line burden and less DLCO.

## PATIENTS AND METHODS

The prospective study was conducted with 77 patients hospitalized due to an acute heart failure diagnosis in the cardiology department of the Ege University Medical Faculty Hospital between January 2018 and December 2018. In the first 24 h after diuretic treatment initiation following the patients' hospitalization, echocardiography data and B-line count by thoracic ultrasonography were recorded. According to the results of thoracic ultrasonography of the patients and the number of B-lines, the patients were divided into two groups: those with <15 B-lines (n=26; 18 males, 8 females; mean age: 48.6±3.3 years; range, 21 to 72 years) and those with >15 B-lines (n=51; 36 males, 15 females; mean age: 53.7±2.0 years; range, 20 to 79 years). The presence of left ventricular ejection fraction >40%, age below 18 and over 80, patients with congenital heart disease, patients who could not undergo optimal echocardiographic examination due to limited echogenicity, patients with a diagnosis of malignancy, patients with severe valve stenosis, and severe chronic disease patients diagnosed with obstructive pulmonary disease and pneumonia were excluded from the study.

After the diuretic treatment was administered to the patients, they were evaluated with a visual analog dyspnea scale and bedside dyspnea test. Patients who did not define dyspnea on the visual analog dyspnea scale and who did not develop dyspnea in the bedside dyspnea test were considered compensated, and the patients who could tolerate the test and did not have contraindications underwent a pulmonary function test, diffusion test, and 6-minute walk test (6-MWT).

Among 77 heart failure patients included in the study, right heart catheterization was applied to the patients deemed necessary to evaluate their suitability for left ventricular support therapy and heart transplantation, and peak oxygen uptake ($pVO_2$) was calculated with metabolic tests. The pulmonary function test results, DLCO, 6-MWT results, echocardiography parameters, right catheterization findings, and $pVO_2$ values were compared between the groups.

Thoracic ultrasonography was performed with GE Healthcare Vivid E9 M5S probe (1.5-4.5 MHz; GE Healthcare Technologies Inc., Chicago, IL, USA) during the first 24 h of hospitalization in the patients included in the study. While evaluating by thoracic ultrasonography, the B-line number was calculated using the method of eight lung zones or four regions for each hemithorax.[10,11] After the B-line number in each region was added together, the patients were divided into two groups, as described above. The presence of pleural effusion was determined during the evaluation with thoracic ultrasonography.

### Statistical analysis

Data were analyzed using IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as numbers and percentages for categorical variables and mean and standard deviation for numerical variables. The Kolmogorov-Smirnov test was used to test whether the variables were normally distributed. Student's t-test was used to compare numerical variables with normal distribution between matched groups, and the Wilcoxon test was used to compare numerical variables that did not show normal distribution. Student's t-test was used to compare quantitative data with normal distribution, and the chi-square test was used to compare qualitative data. While the arithmetic means and standard deviation were presented for numerical variables with normal distribution, median and interquartile range values were shown for those that did not show normal distribution. Pearson's correlation test was used in correlation analysis. A p-value <0.05 was considered statistically significant.

## RESULTS

Those with a B-line number <15 had a mean body mass index of 27.9±1.09 kg/m$^2$), whereas

those with a B-line number >15 had a mean body mass index of 28.2±0.55 kg/m$^2$). In the comparison between the group with the B-line <15 (30% ischemic cardiomyopathy, 69% nonischemic cardiomyopathy, 50% hypertension, 42% diabetes mellitus (DM), 30% atrial fibrillation, and 3% chronic renal failure) and the group with a B-line number >15 (51% ischemic cardiomyopathy, 49% nonischemic cardiomyopathy, 62% hypertension, 41% DM, 37% atrial fibrillation, and 13% chronic renal failure), no significant difference was found in terms of demographic characteristics and comorbid diseases. No significant difference was observed between the group with a B-line <15 (69% ACE [angiotensin-converting enzyme] inhibitor, 19% ARB [angiotensin receptor blocker], 96% beta-blocker, 69% MRA [mineralocorticoid receptor antagonist], 3% ARNI [angiotensin receptor/neprilysin inhibitor], 7% ivabradine, 19% digoxin use history, 7% CRT-D [cardiac resynchronization therapy with defibrillator] implantation) and the group with >15 B-lines (52% ACE inhibitor, 11% ARB, 92% beta-blocker, 64% MRA, 3% ARNI, 13% ivabradine, 13% digoxin use history and 15% CRT-D) in terms of the drugs used by the patients and the treatment applied.

Considering the echocardiography findings performed within the first 24 h after hospitalization in terms of left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrium (LA), and left ventricular end-systolic volume (LVESV) values, no statistically significant difference was found between the group with <15 B-lines (LVEF, 26±0.7%; LVEDD, 6.6±0.16 cm; LVESD, 5.4±0.21 cm; LA, 4.6±0.15 cm; LVESV, 181±13.9 mL) and the group with >15 B-lines (LVEF, 25±0.6%; LVEDD, 6.4±0.12 cm; LVESD, 5.27±0.15 cm; LA, 4.9±0.10 cm; LVESV, 156±7.8 mL).

When the groups with <15 B-lines right ventricular ejection fraction (RVEF), 49±2.06%; ratio of patients with early diastolic transmitral flow velocity/early diastolic mitral anullar velocity (E/e´) >15, 15.4%; LA volume, 29.7±1.09 mL; right ventricular systolic motion (RVSm), 8.9±0.44; tricuspid regurgitant velocity (TRV), 2.8±0.06 m/sec; systolic pulmonary artery pressure (SPAP), 3.08±1.9 mmHg; vena cava inferior (VCI) diameter, 2.08±0.05 cm) and >15 B-lines (RVEF, 41±1.4%; ratio of patients with E/e´ >15%, 62.72%; LA volume, 33.2±0.7 mL; RVSm, 7.5±0.28; TRV, 3.22±0.05 m/sec; SPAP, 55.08±1.4 mmHg; VCI diameter, 2.39±0.03 cm) were compared, RVEF was lower (p=0.003) and the E/e´ ratio was higher in the group with >15 B-lines (p<0.0001). Higher LA volume (p=0.007), lower RVSm (p=0.014), higher TRV (p=0.001), higher SPAP (p<0.0001), and larger VCI diameter (p<0.0001) were determined in the >15 B lines group (Table 1).

When the group with <15 B-lines 15 (30.8% mild tricuspid insufficiency, 61.5% moderate tricuspid insufficiency, 7.7% severe tricuspid insufficiency, 7.7% without mitral insufficiency, 23.1% mild mitral insufficiency, 53.8% moderate mitral insufficiency, and 11.5% severe mitral insufficiencies) and the group with >15 B-lines (11.8% mild tricuspid insufficiency, 64.7% moderate tricuspid insufficiency, 23.5% severe tricuspid insufficiency, 2% without mitral

**Table 1**
Patients' echocardiography findings evaluated in the first 24 h after hospitalization

| Echocardiographic findings | B line <15 (n=26) | B line >15 (n=51) | |
|---|---|---|---|
| | Mean±SD | Mean±SD | *p* |
| LVEF (%) | 26±0.7 | 25±0.6 | 0.185 |
| LVEDD (cm) | 6.6±0.16 | 6.4±0.12 | 0.130 |
| LVESD (cm) | 5.4±0.21 | 5.27±0.15 | 0.255 |
| LA (cm) | 4.6±0.15 | 4.9±0.10 | 0.138 |
| LVEDV (mL) | 248± 17.5 | 209±9.4 | 0.041 |
| LVESV (mL) | 181± 13.9 | 156±7.8 | 0.143 |

SD: Standard deviation; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; LA: Left atrium; LVEDV: Left ventricular end- diastolic volume; LVESV: Left ventricular end-systolic volume.

insufficiency, 7.8% mild mitral insufficiency, 54.9% moderate mitral insufficiency, and 35.3% severe mitral insufficiencies) were compared, no statistically significant difference was observed in terms of tricuspid valve insufficiency, and it was found that the mitral valve insufficiency was more frequent in the group with >15 B-lines (p=0.043, Table 2).

While there was no patient with pleural effusion in thoracic ultrasonography in the group with <15 B-lines, the rate of patients with pleural effusion in the group with >15 B-lines was 19.6%. When the two groups were compared, pleural effusion was observed more frequently in thoracic ultrasonography in the group with >15 B-lines (p=0.014, Table 2).

**Table 2**
Patients' echocardiography findings evaluated in the first 24 h after hospitalization, and thoracic ultrasonographic findings evaluated in terms of pleural effusion

| | B Line <15 (n=26) | | | B Line >15 (n=51) | | | |
|---|---|---|---|---|---|---|---|
| Echocardiographic findings | n | % | Mean±SD | n | % | Mean±SD | *p* |
| RVEF % | | | 49±2.06 | | | 41±1.4 | 0.003 |
| Number of patients with E/e'>15 | 4 | 15.4 | | 32 | 62.7 | | <0.0001 |
| Left atrium volume (mL) | | | 29.7±1.09 | | | 33.2±0.7 | 0.007 |
| RVSm | | | 8.9±0.44 | | | 7.5±0.28 | 0.014 |
| TRV (m/sec) | | | 2.88±0.06 | | | 3.22±0.05 | 0.001 |
| SPAP (mmHg) | | | 43.08±1.9 | | | 55.08±1.4 | <0.0001 |
| VCI diameter (cm) | | | 2.08±0.05 | | | 2.39±0.03 | <0.0001 |
| Mitral insufficiency | | | | | | | 0.043 |
| No | 2 | 7.7 | | 1 | 2 | | |
| Mild | 6 | 23.1 | | 4 | 7.8 | | |
| Moderate | 14 | 53.8 | | 28 | 54.9 | | |
| Severe | 3 | 11.5 | | 18 | 35.3 | | |
| Number of patients with pleural effusion, detected by thoracic ultrasonography | 0 | 0 | | 10 | 19.6 | | 0.014 |

SD: Standard deviation; RVEF: Right ventricular ejection fraction; RVSm: Right ventricular systolic motion; TRV: Tricuspid regurgitant velocity; SPAP: Systolic pulmonary artery pressure; VCI: Vena cava inferior.

**Table 3**
Comparison of the results of the respiratory function test, DLCO, and six-min walk test between the two groups after diuretic treatment

| | B Line <15 (n=26) | B Line >15 (n=51) | |
|---|---|---|---|
| Respiratory function test and DLCO | Mean±SD | Mean±SD | *p* |
| FVC (%) | 78.8±2.86 | 69.6±1.93 | 0.008 |
| FVC (L) | 3320±169.3 | 2507±115 | <0.0001 |
| FEV1 (%) | 76.1±3.02 | 67.7±2.24 | 0.036 |
| FEV1 (L) | 2664±162.7 | 2010±106.4 | 0.002 |
| FEV1/FVC (%) | 93.5±2.45 | 95.6±1.79 | 0.755 |
| PEF (%) | 62.48±3.75 | 58.8±2.94 | 0.346 |
| DLCO (mL/mmHg/min) | 74.6±1.69 | 53.5±1.1 | <0.0001 |
| cDLCO (mL/mmHg/min) | 72.7±1.95 | 49.8±1.39 | <0.0001 |
| Six-minute walk test (meters) | 372.6±14.6 | 220.6±10.5 | <0.0001 |

DLCO: Diffusion test; SD: Standard deviation; FVC: Forced vital capacity; FEV1: Forced expiratory volume during the first seconds; PEF: Peak expiratory flow; cDLCO: Corrected diffusion test.

When the results of respiratory function tests and diffusion test performed after compensation after adequate diuresis were considered, there was no significant difference in forced expiratory volume in 1 sec (FEV1)/forced vital capacity (FVC) and peak expiratory flow (PEF) values between the group with <15 B-lines (FVC, 78.8%±2.86; FVC liter value, 3320±169.3 L; FEV1 percentage value, 76.1±3.02%; FEV1 liter value, 2664±162.7 L; FEV1/FVC ratio, 93%, 5±2.45; PEF, 62.48±3.75%; DLCO, 74.6±1.69 mL/mmHg/min; hemoglobin- and sex-corrected DLCO [cDLCO], 72.7±1.95 mL/mmHg/min) and the group with >15 B-lines (FVC, 69.6%±1.93; FVC liter value, 2507±115 L; FEV1 percentage value, 67.7±2.24%; FEV1 liter value, 2010±106.4 L; FEV1/FVC ratio, 95.6±1.79%; PEF, 58.8±2.94%; DLCO, 53.5±1.1 mL/mmHg/min, cDLCO, 49.8±1.39 mL/mmHg/min). In the group with >15 B-lines, the FVC percentage value was lower ($p=0.008$), the FVC liter value was lower ($p<0.0001$), the FEV1 percentage value was lower ($p=0.036$), the FEV1 liter value was lower ($p=0.002$), the DLCO value was lower ($p<0.0001$), and the cDLCO value was lower ($p<0.0001$). When the group with <15 B-lines (372.6±14.6 m) and >15 B-lines (220.6±10.5 m) were compared, it was observed that the 6-MWT result was lower in the group with >15 B-lines ($p<0.0001$, Table 3).

## DISCUSSION

Today, heart failure incidence has increased, and the lifetime risk of developing heart failure reaches up to 20%. Despite the increasing variety of treatments for heart failure, it is still a disease with high mortality.[17] Heart failure mortality determinants are metabolic test ($pVO_2$), 6-MWT, kidney function tests, N-terminal pro–B-type natriuretic peptide (NT-pro BNP) value, and right ventricular functions. In the latest studies conducted, it is thought that the results of respiratory function tests and diffusion tests may also be determinants of heart failure mortality.

The most important reason for both outpatient clinic admissions and hospitalizations of heart failure patients is dyspnea due to pulmonary edema. To evaluate the patients in terms of pulmonary edema, thoracic ultrasonography, B-line count, and pleural effusion were also added to examinations, such as physical examination findings and chest radiography.

In chronic heart failure, alveolar-capillary membrane changes due to hemodynamic stress caused by increased capillary pressure and changes on the alveolocapillary membrane are irreversible and result in remodeling. Neurohumoral activation due to physical stress caused by increased pulmonary capillary pressure and a decrease in cardiac output stimulates mesenchymal cells and fibrocytes in the interstitium and causes myofibroblasts to proliferate and differentiate. With myofibroblast proliferation, the amount of elastin and collagen begins to increase in the interstitial tissue of the alveolar-capillary membrane, that is, in the extracellular matrix. There is an increase in type 4 collagen and alveolar-capillary membrane thickness. Alveolar-capillary membrane thickening positively reduces pulmonary edema formation; therefore, it protects against increased fluid permeability. However, it causes a decrease in gas diffusion and the formation of restrictive lung syndrome due to increased stiffness, contributing to the development of pulmonary hypertension and a decrease in exercise tolerance. Due to alveolar-capillary membrane thickening, there is a decrease in diffusing capacity in patients with heart failure and a decrease in FVC (restrictive pattern), even if FEV1/FVC is normal. It is thought that the current situation may be the predictor of mortality.[12-16]

In the study conducted by Van Iterson et al.,[18] patients with low DLCO results were found to have lower $pVO_2$ values in the metabolic test result. As a result of the study, it was observed that there was a decrease in the diffusing capacity of patients with moderate and severe heart failure, and the result of DLCO could be a predictor of mortality, similar to $pVO_2$, in heart failure patients. In our study, DLCO was found to be lower in the group with >15 B-lines, and >15 B-lines may be a determinant of mortality, similar to DLCO and $pVO_2$.

Puri et al.[19] administered 10 mL/kg/min 0.9% saline to 10 patients with heart failure, and when the diffusion test results were performed 1 h after the infusion, it was found that the results of alveolar-capillary membrane conductance, FEV1, and peak expiratory flow rates (PEFR) decreased. A saline infusion was given to the patients in the healthy control group, and no change was detected in the respiratory function test and diffusion test performed 1 h later.

Similar results were obtained in our study, and it was observed that the results of DLCO, FVC, and FEV1 were lower in those with >15 B-lines (extravascular fluid retention in the lung). It was observed that the results of DLCO, FVC, and FEV1 might be lower as a result of the increase in alveolar-capillary membrane thickness due to hemodynamic stress caused by excessive extravascular fluid retention.

When another study of Puri et al.[20] was examined, alveolar-capillary membrane diffusive capasity, DLCO, and alveolar volume decreased in the group with heart failure compared to healthy individuals. Although healthy individuals were not included in our study, it is thought that patients with >15 B-lines may have had increased alveolar-capillary membrane thickness, and as a result, DLCO was found to be lower due to decreased permeability.

Morosin et al.[21] found that $pVO_2$, FEV1, and FVC were lower in the group with DLCO <80% compared to those with DLCO >80% in patients with stable heart failure. Similarly, in our study, FVC and FEV1 were low together with DLCO in the group with >15 B-lines.

Melenovsky et al.[22] included 186 heart failure patients and 21 healthy control group patients in their study. Pulmonary radiographs of heart failure patients were interpreted and grouped as the wet lung group with a congestion score index >0.5 (n=74) and the dry lung group with a congestion index score <0.5 (n=112). Right catheterization, respiratory function tests, diffusion tests, and echocardiography were applied to the wet and dry lung groups. When all findings were compared between the two groups, FVC and DLCO were lower in the heart failure group with wet lungs. When the two groups were compared in terms of FEV1/FVC, it was found that there was no significant difference. Furthermore, in the heart failure group with wet lungs, pulmonary artery compliance was lower, pulmonary vascular resistance and pulmonary stub pressures were higher, right ventricular functions were lower, DLCO results were lower, and a restrictive pattern was observed in the pulmonary function test. In their median follow-up of 333 (interquartile range 80-875) days, it was shown that mortality increased in the wet lung group. In our study, in the group with >15 B-lines, right ventricular functions were found to be lower, DLCO was lower, pulmonary vascular resistance was higher, and a restrictive pattern was observed due to the pulmonary function test. It was observed that there is a significant correlation between the results of our study and the results of the study conducted by Melenovsky et al.[22]

In the study conducted by Coiro et al.,[23] it was determined that the patient group with >30 B-lines had higher mortality, and hospitalization was more frequent as a result of thoracic ultrasonography performed before discharge in heart failure patients. In our study, follow-up could not be performed with mortality and rehospitalization, but in the group with >15 B-lines, DLCO was lower, right ventricular functions were higher, the rate of patients with E/e´ >15% was higher, VCI diameter was more dilated, and pulmonary vascular resistance pressure was higher. These findings are accepted as an indicator of a poor prognosis.

In the CHAMPION study, a device that can measure pulmonary artery pressure with CardioMEMS was evaluated by implanting. In the device follow-up, it was observed that the mean pulmonary artery and pulmonary stub pressure increased during the process from dry lung to pulmonary edema, and if the pulmonary edema picture increased more in the follow-up of DLCO followed by FVC, FEV1/FVC decreased.[24] In our study, DLCO and FVC were low in patients with >15 B-lines (pulmonary edema), but FEV1/FVC decreased.

In the study conducted by Platz et al.,[25] thoracic ultrasonography was examined by an eight-region scanning method before discharge in heart failure patients. It was observed that patients with >3 B-lines had higher mortality and rehospitalization rates. In our study, mortality was not calculated, but in the group with >15 B-lines, the right ventricular function was found to be more suppressed, DLCO was lower, and pulmonary vascular resistance was higher, which could be a predictor of mortality.

In the study by Agostoni et al.,[16] heart failure patients were subjected to metabolic testing and grouped as <12, 12-16, and 16-20 according to the $pVO_2$ results. In the group with $pVO_2$ <12, DLCO, alveolar volume, capillary volume, and alveolar-capillary membrane diffusive capasity were lower than in the other groups. Similarly, in our study, the 6-MWT, performed to evaluate functional capacity, and the DLCO were lower in the group with >15 B-lines.

There are some limitations to this study. Short- and long-term follow-up of the patients after discharge from the hospital in terms of mortality and rehospitalization frequency would have been beneficial to the study. Identifying the effect of a B-line number >15 on mortality and hospitalization frequency could support the study results. Although it was not included in our study's method, a higher number of patients who underwent right heart catheterization and had measured right atrial pressure/left atrial pressure, pulmonary arterial pressure, and pulmonary vascular resistance values could contribute to the study. Checking the number of B-lines by thoracic ultrasonography during diffusion tests and before discharge could provide the accuracy of the study results and a better determination of the congestion status of the patients.

In conclusion, a B-line number >15 alone may be predictive in terms of decreased diffusion capacity, decreased right ventricular function, increased pulmonary vascular resistance, and restrictive pattern in respiratory function. There are poor prognosis indicators, such as a 6-MWT and right ventricular function for heart failure. In the group with a B-line number >15, decreased DLCO as a result of decreased six-min walking capacity, more pressure on right ventricular functions, and lower follow-up DLCO suggests that it may be an indicator of poor prognosis in heart failure.

**Ethics Committee Approval:** The study protocol was approved by the Ege University Faculty of Medicine Ethics Committee (date: January-December 2018, no: 18-2.1/31). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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