# Evaluation of the Relationship Between Estimated Right Atrial Pressure and Fibrosis-4 Index in Patients with Congenital Heart Disease

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## Abstract

**Aim:** The fibrosis-4 index is a non-invasive and reproducible approach to assess liver stiffness (LS). LS has been reported to be associated with fibrosis but mean right atrial pressure can also influence LS values. We aimed to evaluate the relationship between fibrosis-4 index and echocardiographically estimated right atrial pressure in adults with congenital heart disease.

**Methods**: This study was conducted at a tertiary heart center between January 2021 and January 2023. A total of 127 patients with congenital heart disease were included in the study. The fibrosis 4 index was calculated. The fibrosis-4 index was calculated as follows: Fibrosis-4 index = age (years) × AST (U/L)/[ALT (U/L)1/2 × platelet count (109/L)](14). Echocardiographic measurements were analyzed. The inferior vena diameter and collapsibility index were calculated and the estimated right atrial pressure was evaluated.

**Results:** Study patients included 75 women (59%) with a mean age of 50 ± 9.9 years. Fibrosis-4 index was significantly correlated with TRV max (r = 0.51, p < 0.001), estimated right atrial pressure (r = 0.63, p < 0.001), estimated systolic pulmonary artery pressure (r = 0.42, p < 0.001), IVC diameter (r = 0.62, p < 0.001), IVC collapsibility (r = 0.464, p < 0.001), and NT-proBNp value (r = 0.624, p < 0.001). The fibrosis-4 index was also significantly correlated with the degree of tricuspid valve insufficiency(r = 0.342, p < 0.001), RV basal diameter (r = 0.294, p = 0.001), ASD diameter(r = 0.27, p = 0.002), Qp/Qs (r = 0.271, p = 0.003). However; the fibrosis 4 index was not significantly correlated with high-sensitive troponin (r = 0.11, p = 0.43). The fibrosis-4 index greater than 1.23 was associated with increased estimated right atrial pressure (IVC diameter > 21mm and IVC collapsibility < 50%), with a sensitivity of 95 % and a specificity of 74 % (AUC= 0.88; p<0.001; 95% CI: 0.82-0.94).

**Conclusions**: The fibrosis-4 index, which is a marker of liver congestion/stiffness/fibrosis, may be an important indicator in the echocardiographic determination of estimated mean right atrial pressure and the possibility of pulmonary hypertension in patients with congenital heart disease.

***Keywords:*** *Congenital heart disease, estimated mean right atrial pressure, fibrosis-4 index, liver stiffness*

## 1. Introduction

The spectrum of chronic liver damage attributed to passive hepatic congestion that occurs in the setting of any cardiopulmonary disease that causes increased central venous pressure (right atrial pressure), such as right-sided heart failure, is referred to as congestive hepatopathy[1]. Common causes include biventricular insufficiency due to cardiomyopathy, severe pulmonary hypertension, right ventricular myocardial infarction, constrictive pericarditis, cor pulmonale, mitral valve stenosis, and valvulopathies such as tricuspid valve regurgitation. Since the pressure from the right ventricle is transmitted directly to the hepatic veins and sinusoids, insufficiency of the tricuspid valve causes passive congestion. If left untreated, long-standing congestion can lead to cardiac fibrosis and eventually cardiac cirrhosis[1].

There are approximately 1 million adult patients with congenital heart disease (CHD) in the United States, and the number is increasing[2]. Hepatic complications are common and may occur secondary to persistent chronic passive venous congestion or decreased cardiac output resulting from the underlying cardiac disease or as a re-

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sult of palliative cardiac surgery; transfusion or drug-related hepatitis may also occur. The unique physiology of Fontan circulation is particularly prone to the development of hepatic complications and is, in part, related to the duration of the Fontan procedure. Liver biochemical test abnormalities may be related to cardiac failure, resulting from intrinsic liver disease, secondary to palliative interventions, or drug-related[2,3].

Liver dysfunction is one of the important non-cardiac complications of CHD. According to an analysis of the German National CHD Register, it was observed in 6% of deceased patients suffering from CHD[4]. In a study, it was shown that cirrhosis occurred 11-15 years after Fontan surgery in patients under the age of 25[5]. For this reason, it is recommended to monitor non-cardiac complications, especially liver dysfunction[3,6,7].

Elevated mean right atrial pressure (RAP) measured by right heart catheterization is an established risk factor for poor survival in the Registry to Evaluate Early and Long-term pulmonary arterial hypertension Disease Management (REVEAL Registry) as well as other cohorts[8,9]. Echocardiography estimates of right atrial pressure have been validated against right heart catheterization in the general population and have shown a modest correlation in patients with pulmonary arterial hypertension[8,10]. While several methods have been studied, assessment of the inferior vena cava (IVC) diameter and percent collapsibility with inspiration or "sniff" is the most widely used and accepted[8,10,11].

Non-invasive liver stiffness value of liver ultrasonography determines the average mean RAP independently in patients with and without heart failure. LS measurement was thought to be a cheap, simple, and non-invasive follow-up parameter that could be used to adjust the volume status and the dose of diuretic therapy in the routine follow-up of patients with heart failure. According to previous studies and our study results, >7 kPa value for liver stiffness determined in liver ultrasonography may be predictive for increased mean RAP[12].

The fibrosis-4 index is expressed as a cheap, easy, and simple index to evaluate liver stiffness, and liver fibrosis[13-15]. The fibrosis-4 index consists of four parameters. These parameters are aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, and age[13-15]. Fibrosis-4 index formulated as = age (years) × AST (U/L)/[ALT (U/L)1/2 × platelet count (109/L)](14). The fibrosis-4 index was stated to reflect liver stiffness/fibrosis associated with viral hepatitis of hepatitis C virus or human immunodeficiency virus infection and non-alcoholic fatty liver disease[13-15]. In studies conducted on patients with heart failure, it was found that fibrosis-4 index and all-cause mortality increased significantly as right atrial pressure and pro-brain natriuretic peptide increased[16-18]. Recently, the fibrosis-4 index is considered to be a surrogate marker to assess the prognosis and the severity of venous congestion in patients with heart failure[16-18]. In our study, we examined the relationships between the fibrosis-4 index and echocardiographic parameters, including estimated right atrial pressure, tricuspid valve regurgitation maximum velocity, inferior vena cava diameter, and collapsibility index.

## 2. Materials and methods

This study was conducted at a tertiary heart center between January 2021 and January 2023. A total of 127 patients with CHD were included in the study. 103 (81%) of these patients had atrial septal defect (ASD), 21 (20%) had ventricular septal defect (VSD), and 3 (3%) had patent ductus arteriosus (PDA). Of the patients with ASD, 90 (87%) were secundum type ASD, 11 (11%) were sinus venosus type ASD, and 2 (2%) were primum ASD. Patients with known acute or chronic liver disease, hepatitis, left-sided heart failure, significant left-sided valve insufficiency, obstructive and restrictive lung diseases, and use of liver toxic agents were not included in the study. Detailed medical records were reviewed and recorded. Blood samples of all patients were collected. Routine biochemical parameters, including liver function tests, were analyzed and recorded. The fibrosis 4 index was calculated. The fibrosis-4 index was calculated as follows: Fibrosis-4 index = age (years) × AST (U/L)/[ALT (U/L)1/2 × platelet count ($10^9$/L)][14].

All patients underwent a comprehensive transthoracic echocardiography including two-dimensional and Doppler echocardiography. All patients were breathing spontaneously without mechanical ventilation and did not require vasopressor support. Images of the IVC were obtained via the subcostal window. Measurements were analyzed by a single operator with direct supervision by an echocardiographer who was blinded to clinical information. The echocardiographer was blinded to the fibrosis-4 index. From the apical approach, we measured tricuspid lateral annular systolic velocity (Sm), and the tricuspid annular plane systolic excursion (TAPSE) to assess right ventricular function. TAPSE was measured by the distance of the systolic excursion of the right ventricle annulus along its longitudinal plane using M-mode presentation in a right ventricle-focused apical 4-chamber view. Sm was measured by the velocity of the tricuspid lateral annular using Doppler tissue imaging in a right ventricle-focused apical 4-chamber view. The left ventricular ejection fraction (%) was measured by the modified Simpson technique using B-mode presentation in apical-2-chamber view and apical-4-chamber view. We also measured the peak early diastolic velocities (E), and the early diastolic myocardial velocities (Em) using general methods. The ratio of E and Em (E/Em) was calculated to estimate left ventricular filling pressures[19].

The IVC diameter was measured in the long axis within 1 to 2 cm of the junction with the right atrium during normal respiration as well as inspiratory sniff. The collapsibility index was calculated as; Collapsibility index = (Minimum IVC diameter during sniff / Maximum IVC diameter during normal respiration) X 100. Estimated RAP using the collapsibility index and maximum IVC diameter were used to categorize the patients into groups of increasing estimated RAP as defined by the 2019 American Society of Echocardiography guidelines[19,20]. If IVC diameter < 21mm and IVC collapsibility > 50%, the estimated right atrial pressure was evaluated as 3 mmHg (0-5), and if IVC diameter > 21 mm and IVC collapsibility < 50%, the estimated right atrial pressure was evaluated as 15 mmHg (10-20). In other cases, the estimated right atrial pressure was evaluated as 8 mmHg[5-10,19,20].

Doppler measurements were used to estimate systolic pulmonary artery pressure (PAP). Estimated systolic PAP was calculated by adding peak tricuspid regurgitation velocity and right atrial pressure. The simplified Bernoulli equation, estimated systolic PAP = 4(TRV max)2 + estimated mean RAP, was used (TRV max is the estimated Doppler peak velocity (m/s) across the tricuspid valve, provided there is no right ventricular outflow tract obstruction)[19,20].
TRV max value was used to estimate the probability of pulmonary hypertension (PH). If this value is less than ≤2.8 m/s or cannot be measured, then it is unlikely to suggest PH. If TRV max is between 2.9-3.4 m/s, the index of suspicion increases. This is even more likely if TRV max is >3.4 m/s without other signs of PH. The probabilities were then used to determine whether cardiac catheterization was necessary in individual patients[21,22].
All data were numerically encoded. For statistical analysis, they were entered into the SPSS 22.0 computer software package and scanned for variable and case-by-case missing values. Quantitative data were expressed as mean ± standard deviation. Qualitative data were compared between groups using the chi-square test. Pearson and/or Spearman correlation analyses were performed between

the fibrosis-4 index and echocardiographic parameters such as estimated RAP and TRV max, and correlation graphs were obtained. ROC curve analysis of TRV max and estimated RAP with Fibrosis-4 index was performed and graphs were obtained.

The Institutional Review Board of our Hospital approved this study (study approval number: 12-2020-2146). Written informed consent to participate in the study was obtained from all participants. The principles of the study are in accordance with the Declaration of Helsinki

## 3. Results

Table 1 shows the clinical characteristics of all patients. Study patients included 75 women (59%) with a mean age of 50 ± 9.9 years. Table 1 shows laboratory data from the day of admission. In our study, the fibrosis index 4 was significantly higher in increased estimated right atrial pressure, higher TRV max, increased estimated systolic pulmonary artery pressure, and increased IVC diameter. Fibrosis 4 index was significantly correlated with TRV max ($r = 0.51$, $p < 0.001$) (figure 1a), estimated right atrial pressure ($r = 0.63$, $p < 0.001$) (figure 1b), estimated systolic pulmonary artery pressure ($r = 0.42$, $p < 0.001$) (figure 1c), IVC diameter ($r = 0.62$, $p < 0.001$) (figure 1d), IVC collapsibility ($r = 0.464$, $p < 0.001$), and NT-proBNp value ($r = 0.624$, $p < 0.001$). The fibrosis 4 index was also significantly correlated with the degree of tricuspid valve insufficiency($r = 0.342$, $p < 0.001$), RV basal diameter ($r = 0.294$, $p = 0.001$), ASD diameter($r = 0.27$, $p = 0.002$), Qp/Qs ($r = 0.271$, $p = 0.003$). However; the fibrosis 4 index was not significantly correlated with high-sensitive troponin ($r = 0.11$, $p = 0.43$). The fibrosis 4 index greater than 1.07 was associated with high TRV max (TRV max > 3.4 m/s), with a sensitivity of 81 % and a specificity of 74 % (Area under the ROC curve= 0.84; $p<0.001$; 95% CI: 0.74-0.94) (Figure 2a).

**Table 1**

Baseline clinical characteristics of this study

| Variables | *n* = 127 |
|---|---|
| Age, years | 50 ± 9.9 |
| Female, n (%) | 75 (59) |
| Body mass index, kg/m$^2$ | 22.9 ± 4.2 |
| Systolic blood pressure, mmHg | 121.8 ± 18.8 |
| Heart rate, b.p.m. | 69.3 ± 14.5 |
| Hypertension, n (%) | 15 (11.8) |
| Diabetes mellitus, n (%) | 2 (1.6) |
| Atrial fibrillation, n (%) | 6 (4.7) |
| Prior percutaneous coronary intervention, n (%) | 3 (2.4) |
| Beta-blockers, n (%) | 16 (12.6) |
| Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers, n (%) | 7 (5.5) |
| Left ventricular ejection fraction, % | 62.7 (55.9–68.6) |
| Early diastolic filling velocity/early diastolic velocity of the mitral annulus | 5.4 (4.0–7.1) |
| Tricuspid annular plane systolic excursion, mm | 21.5 ± 4.6 |
| Tricuspid lateral annular systolic velocity, cm/s | 12.2 (10.0–14.6) |
| Inferior vena cava diameter, mm | 19.6 ± 3.4 |
| Maximum tricuspid regurgitation jet velocity (TRV max), m/s | 2.87 ± 0.48 |
| Estimated systolic PAP, mmHg | 40.2 ± 15.8 |
| Qp/Qs | 1.73 ± 0.48 |

*Notes:Data are presented as the number (%), mean ± standard deviation, or median (25th–75th percentile).*

**Figure 1**

Scatter-dot plot showing the correlation of fibrosis 4 index with TRV max (figure 1a), estimated right atrial pressure (figure 1b), estimated systolic pulmonary artery pressure (figure 1c) and IVC diameter (figure 1d), respectively.

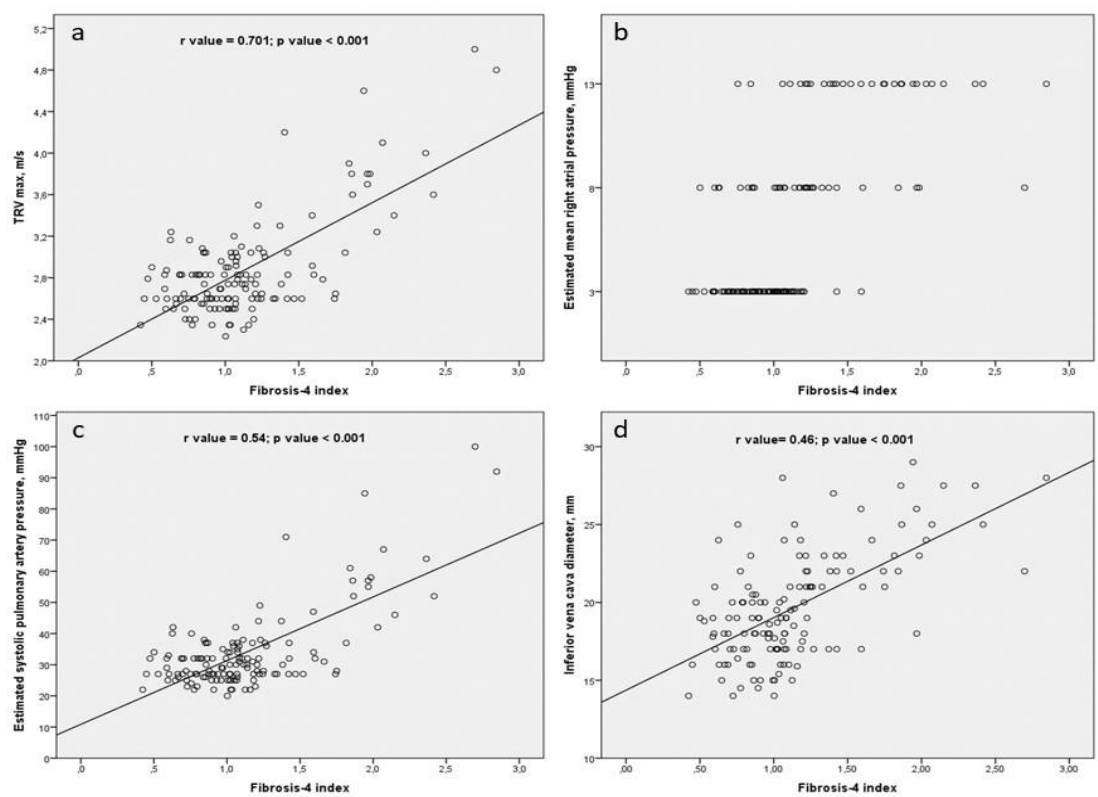
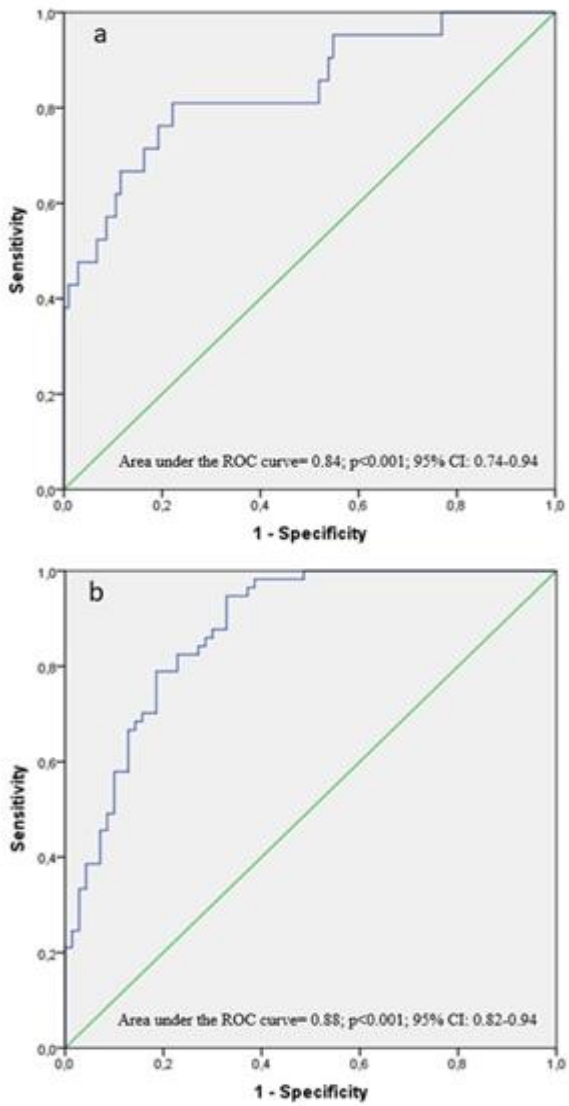


Figure 2

ROC analysis showing the relationship between fibrosis 4 index and TRV max (figure 2a), and estimated right atrial pressure (figure 2b), respectively.




The fibrosis 4 index greater than 1.23 was associated with increased estimated right atrial pressure (IVC diameter > 21mm and IVC collapsibility < 50%), with a sensitivity of 95 % and a specificity of 74 % (Area under the ROC curve= 0.88; p<0.001; 95% CI: 0.82-0.94) (Figure 2b).

The HALP score was statistically higher in NSTEMI group compared to NCA group (7.3 (5.1 – 10.0) for NSTEMI group and 5.1 (3.9 – 6.4) for NCA group, p<0.001). The main characteristics of the patient groups are shown in Table 1.

The binary logistic regression analysis was used to evaluate the impact of risk factors and laboratory parameters on NSTEMI patients. Age and HALP score have explanatory powers on NSTEMI patients (p=0.001 and p=0.022, in order of) (Table 2).

ROC curve analysis was formed to predict the best cut off value for HALP to predict NSTEMI in patients. The area under the curve was 0.706 which is an acceptable value. Best cut of value was 5.58 with 69.7% sensitivity and 62.5% specificity (Figure 2).

Table 2

Visual acuity and geriatric depression scale results before and after surgery

| Variable | On admission |
|---|---|
| Haemoglobin, g/dL | 12.4 ± 2.1 |
| Platelet count, 109/L | 264.3 ± 60.2 |
| Prothrombin time, s | 12.7 ± 2.3 |
| Total Bilirubin, mg/dL | 0.64 ± 0.32 |
| Aspartate aminotransferase, IU/L | 23.1 ± 7.1 |
| Alanine aminotransferase, IU/L | 17.9 ± 9.0 |
| Fibrosis-4 index | 1.13 ± 0.45 |
| Total bilirubin, g/dL | 0.8 (0.5–1.2) |
| Albumin, g/dL | 42.7 ± 3.7 |
| Serum creatinine, mg/dL | 0.8 (0.5–1.1) |
| N-terminal pro-brain natriuretic peptide, pg/mL | 700 (30–730) |
| High sensitivite troponin, | (1–48) |

*Notes:Data are presented as the number (%), mean ± standard deviation, or median (25th–75th percentile).*

## 4. Discussion

In patients with CHDs, this study showed a significant correlation between the Fibrosis 4 index and echocardiographic estimated right atrial pressure (based on inferior vena diameter and collapsibility rate) or the estimated probability of pulmonary hypertension (based on TRV max) (figure 1, 2). In addition, the ROC analyses performed in this study found that the Fibrosis 4 index was quite sensitive and specific in showing echocardiographic increased right atrial pressure (via inferior vena diameter and collapsibility rate) or the possibility of high pulmonary hypertension (via TRV max) (figure 1, 2).

Liver tissue biopsy remains the reference standard for assessing the severity of diseases that directly or indirectly affect the liver. Currently, a variety of non-invasive methods are used to quantify liver fibrosis, including serum biomarkers and imaging techniques. Fibrosis-4 index, which is calculated with four parameters including age, ALT, AST, and platelet count, is among these methods. Fibrosis-4 index has been used as a surrogate marker of liver stiffness[14]. A recent comparative study by Forsgren MF and colleagues involving chronic liver diseases such as nonalcoholic fatty liver disease and chronic hepatitis C demonstrated that the diagnostic performance of magnetic resonance imaging, transient elastography, and fibrosis-4 index in predicting significant fibrosis was sufficiently accurate[23]. Therefore, the fibrosis-4 index may be a marker of liver fibrosis or stiffness in chronic liver disease.

The fibrosis-4 index is considered a simple biomarker of liver fibrosis in patients with liver diseases. However, the liver may become stiff because of long-term hepatic congestion and accompanying fibrosis in patients with ASD. Furthermore, liver stiffness measured by transient elastography increases as the central venous blood pressure increases[24].

Estimation of intravascular volume is very important, as it is a critical component for optimal patient care and management. RAP provides relevant clinicians with important information about their patients regarding the estimation of intravascular volume. Increased RAP is associated with adverse outcomes and is independently associated with all-cause mortality in patients with cardiovascular disease. The gold standard method for assessing RAP (or central venous pressure) remains invasive monitoring. However, various techniques are available for noninvasive evaluation of RAP. Various echocardiographic methods consisting of indices obtained from inferior vena cava diameter, inferior vena cava collapsibility index, hepatic veins, tissue Doppler parameters and right

atrial dimensions have been proposed for the noninvasive evaluation of RAP[25].

Jalal Z et al stated that liver stiffness measurement using Transient elastography is a rapid and reliable method to evaluate central venous pressure in patients with CHD. We compared the echocardiographic estimated RAP, which is an indirect indicator of invasively measured central venous pressure, which is an indicator of mean RAP, and the fibrosis 4 index, which can predict liver stiffness, and found that there is a significant relationship between these parameters[26].

PH occurs in approximately 10% of adult patients with CHD. PH is a relatively common complication in patients with CHD. PH in CHD patients is often associated with left-to-right shunt defects. Additionally, PH may develop secondary to left heart obstructive disease causing postcapillary hypertension in CHD[27]. Common congenital heart diseases include ASD, VSD, and PDA. PH and right heart failure are more common in ASD patients with large defects, undiagnosed for a long time, or without defect closure. Right ventricular dysfunction exacerbates the clinical findings of right heart failure. Sm and TAPSE are both indices of right ventricular contraction in the longitudinal plane. It provides sufficient data about right ventricle systolic dysfunction[28]. Saito Y et al demonstrated that liver stiffness, measured by transient elastography, increased with a decrease in TAPSE. They also demonstrated that a high fibrosis-4 index was associated with lower TAPSE and Sm. For this reason, the fibrosis-4 index can be regarded as a biomarker for right ventricular dysfunction in adult patients with ASD[29]. Our study showed that there is a significant relationship between TRV max and fibrosis-4, which contributes to predicting the possibility of PH echocardiographically. We also found that there was a correlation between estimated systolic pulmonary artery pressure and fibrosis-4 index. In our study, there were almost no patients with severe liver fibrosis/stiffness because the number of patients with severe right ventricular dysfunction or severe pulmonary arterial hypertension, including Eisenmenger syndrome, was very low. Examining this relationship in a large patient population, including patients with severe pulmonary arterial hypertension and/or right ventricular dysfunction in different types of CHD (sub)groups, may provide more accurate results. In a study published by Kerkütlüoğlu M., the fibrosis-4 index is stated as an independent prognostic indicator in pulmonary arterial hypertension patients. However, he claimed that the Fibrosis-4 index, a simple, cost-effective, and easily accessible tool, could be used to predict both survival rates and disease severity in individuals suffering from pulmonary arterial hypertension[30]. Although our study is not a prognosis study, the fibrosis-4 index may have prognostic value in congenital heart patients, as mean right atrial pressure and systolic pulmonary artery pressure have prognostic value in patients with pulmonary arterial hypertension. Further studies are required for this.

### Limitation

This study had several limitations. First, this study was a retrospective cohort study at a single tertiary center, and the study had a relatively small sample size. Second, we did not perform additional examinations such as liver biopsy or computed tomography scans for evaluation. chronic liver diseases were not completely ruled out.

## 5. Conclusion

The fibrosis-4 index, which is a marker of liver congestion/stiffness/fibrosis, may be an important indicator in the echocardiographic determination of estimated mean RAP and the possibility of PH in patients with CHD. A more comprehensive study, including invasive right heart catheterization parameters and prognosis data, is needed to support these results.

## Statement of ethics

The study was approved by the local ethics committee Hospital approved this study (study approval number: 12-2020-2146).

## Conflict of interest statement

The author declares that they have no financial conflict of interest with regard to the content of this report.

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