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Fibrosis-4 Index as an Independent Predictor of Mortality in Pulmonary Arterial Hypertension

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Abstract

Objectives: Liver fibrosis is independently associated with pulmonary arterial hypertension (PAH). Investigating the relationship between liver fibrosis and PAH may provide mechanistic insight into this relationship. In this study, we aimed to elucidate the relationship between the fibrosis-4 (Fib-4) index and PAH.

Materials and Methods: In this retrospective, single-center cohort study, 61 patients diagnosed with PAH were included. During a median follow-up period of 27 months, Fib-4 indexes calculated from alanine aminotransferase, partate aminotransferase, and platelet values at the time of PAH diagnosis were evaluated in patients who experienced mortality and survived.

Results: During the subsequent evaluation of the study cohort, 20 patients were found to have experienced mortality. The group with mortality had higher Fib-4 scores (1.6±0.22 vs. 0.69±0.4, p=0.003). Independent predictors of mortality and the diagnostic performance of the Fib-4 index were analyzed by ROC curve analysis. Accordingly, the predictive value of the Fib-4 index for mortality was >1.02, with a sensitivity of 77% and specificity of 72% (area under the curve: 0.824, 95% confidence interval: 0.740-0.880).

Conclusion: The Fib-4 index, a straightforward and valuable metric, can be used as a prognostic marker for mortality in patients with PAH.

Keywords: Fibrosis-4 index, liver dysfunction, mortality, pulmonary arterial hypertension

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Introduction

Pulmonary arterial hypertension (PAH) is a debilitating condition characterized by gradual deterioration and restructuring of the pulmonary arteries, ultimately leading to right ventricular failure and mortality[1]. In the absence of therapeutic intervention, the median survival duration is observed to be less than three years[2]. In recent years, the management of PAH has experienced a remarkable transformation, leading to notable advancements in patient survival rates[3]. Nevertheless, PAH continues to be a relentless and lethal condition, particularly for individuals classified as World Health Organization functional class (WHO FC) III or IV. These patients face a substantially heightened risk of experiencing severe right heart failure or sudden cardiac death, which is in stark contrast to those classified as class I or II[4]. This phenomenon could be ascribed, at least in part, to the interplay between PAH and various other bodily organs[5].

Liver function abnormalities frequently occur in individuals with heart failure and are associated with an unfavorable prognosis[6]. Passive congestion and impaired perfusion of the liver, which are considered to be the causative mechanisms of cardiac syndromes, may be observed in patients with PAH[7]. To date, a limited number of studies have shed light on the impact of bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) on PAH[8]. The aforementioned studies propose that hyperbilirubinemia may serve as a potential indicator for assessing the severity and prognostic outcomes of patients diagnosed with PAH. However, several indices of liver performance have been neglected.

The fibrosis-4 (Fib-4) index is a commonly employed diagnostic tool for the evaluation and measurement of liver fibrosis[9,10]. Hence, the present study was conducted with the aim of elucidating the distinctive pattern exhibited by the Fib-4 index in a carefully defined group of consecutive patients diagnosed with PAH. In addition, we sought to assess the potential correlation between the Fib-4 index and survival rates among individuals affected by PAH.

Materials and Methods

A retrospective evaluation was conducted on a cohort of 84 consecutive patients, ranging in age from 18 to 65 years, who were diagnosed with newly onset PAH at the Clinic of Cardiology, Kahramanmaraş Sütçü İmam University Faculty of Medicine Hospital. The evaluation period spanned from January 2015 to July 2022. The exclusion criteria were as follows: patients presenting with different types of pulmonary hypertension, along with a medical history encompassing hepatobiliary disorders, chronic nephritis, chronic renal impairment, or concurrent malignancy, as well as a past record of alcohol abuse and potential hepatotoxic medication or drug-induced liver dysfunction. Based on the exclusion criteria, 61 patients were deemed eligible for inclusion in the present study. Epidemiological, demographic, and clinical data, treatment, right heart catheterization (RHC), and Fib-4 score were extracted from the medical records using a standardized data collection form. RHC was performed to confirm the existence of PAH, a condition distinguished by a mean pulmonary arterial pressure (mPAP) that meets or exceeds 25 mmHg, a pulmonary artery wedge pressure (PAWP) of 15 mmHg or lower, and a pulmonary vascular resistance (PVR) that exceeds 3 wood units. After excluding alternative etiologies for PAH, the determination of idiopathic PAH was made by a minimum of two proficient PAH specialists, adhering to the guidelines of the 2015 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) for Pulmonary Hypertension[2]. The 6-minute walk distance (6MWD) assessment was conducted in adherence to the guidelines set forth by the American Thoracic Society[11]. Measurements of right atrial pressure (RAP), PAP, PAWP, PVR, and cardiac output (CO) were determined using the Fick method. The determination of the cardiac index (CI) involved the computation of the ratio between CO and body surface area.

The primary outcome measure of this investigation encompassed the incidence of mortality, with diligent

monitoring of patients over a mean duration of 27 (6-68) months. To evaluate the patients' survival, diligent observation was conducted by the study investigators either during outpatient clinic visits, through telephone interviews, or by accessing the national health record system. This meticulous monitoring continued until the event of death occurred. A total of 20 individuals, constituting approximately 32% of the overall study cohort, encountered mortality incidents over the course of the designated observation period.

The study cohort was stratified into two distinct cohorts on the basis of their respective outcomes, namely mortality and survival. The Fib-4 index (Age x AST)/(Platelets x √ALT) was computed for each individual in the study cohort. The objective of this study was to assess the predictive capability of the Fib-4 index in terms of mortality outcomes. The study was conducted in accordance with the Declaration of Helsinki on Human Research and approved by the Kahramanmaraş Sütçü İmam University Faculty of Medicine Ethics Committee (approval number: 01, date: 24.01.2023).

Statistical Analysis

The data management and analysis procedures were executed using SPSS software version 24 (SPSS Inc., Chicago, IL, USA). A p-value of ≤0.05, indicating statistical significance, was observed on both sides. Categorical variables are commonly presented by providing the count and percentage of cases, whereas continuous variables are typically represented by the mean ± standard deviation (or median and interquartile range. The statistical analysis encompassed the application of two distinct methodologies for comparing means: the independent sample t-test and, in instances where the data deviated from a normal distribution, the Mann-Whitney U test with median. The chi-square test was used, as deemed appropriate, for evaluating categorical data. A correlation analysis was performed using the Pearson correlation test for variables that demonstrated a normal distribution, whereas the Spearman correlation test was used for variables that did not adhere to a normal distribution. The optimal threshold value for the Fib-4 index in predicting mortality was determined using receiver operating characteristic (ROC) curve analysis. The computation of the area under the curve (AUC), accompanied by a 95% confidence interval, was performed to evaluate the prognostic significance of mortality. Univariate analysis was used to evaluate the association between variables and mortality. Variables that exhibited statistical significance in the univariate analysis, in addition to other potential confounding factors, were included in a multivariate logistic regression model using the backward stepwise approach. The objective of this study was to determine the independent prognostic factors associated with mortality.

Results

Out of the entire cohort consisting of 84 individuals, a subgroup of 23 patients (comprising 11 individuals with a medical history of hepatobiliary disease, 4 patients with drug-induced liver dysfunction, 1 patient with a history of alcohol use, 3 patients with chronic hepatitis, and 4 patients with chronic renal failure) were deemed ineligible for inclusion in the study because of predetermined exclusion criteria. In this particular investigation, 61 patients diagnosed with PAH were selected as participants. The average age of the patients in the study was found to be 67±11 years. Mortality was documented in a cohort of 20 patients over an average duration of 27 (6-68) months, determined through diligent follow-up. The average age of individuals in the group who experienced mortality was found to be significantly higher (57±8 vs. 40±17, p=0.001). The study patients' baseline characteristics and laboratory findings are presented in Table 1. Among the cohort of patients who experienced mortality, it was observed that 60% (n=12) were of the male gender. In addition, 45% of these patients were classified under the WHO FC I/II category, while the remaining 55% were categorized under WHO FC III/IV. Patients who experienced mortality during the follow-up period exhibited elevated levels of B-type natriuretic peptide (BNP) at the time of PAH diagnosis (3.738±1.384 vs. 860±204, p=0.003).

Table 1. Baseline characteristics of study patients

	Survivor (n=41)	Mortality (n=20)	p-value
Baseline characteristics			
Age, years	40±17	57±8	0.001
Male	26 (63%)	12 (60%)	0.573
BMI, kg/m²	27.3±2.9	27.7±3.8	0.692
WHO FC			0.512
Class 1-2	22 (53%)	9 (45%)	
Class 3-4	19 (47%)	11 (55%)	
6MWD, m	427±116	307±127	<0.001
Laboratory findings			
Creatinine, mg/dL	0.81±0.33	0.88±0.37	0.43
Alanine aminotransferase, U/L	20.5±13.9	32.3±22.8	0.04
Aspartat aminotransferase, U/L	25.5±16.4	41.4±21.8	0.02
Sodium, mmol/L	139.7±4.1	137.5±5.8	0.144
Potassium, mmol/L	4.4±0.4	4.3±0.5	0.831
Calcium, mg/dL	9±0.5	8.5±0.8	0.320
Magnesium, mg/dL	1.9±0.7	1.7±0.2	0.145
Troponin, ug/L	0.21±0.09	0.53±0.31	0.347
Hemoglobin, g/dL	13.9±2.1	13.1±2.9	0.280
Hematocrit, %	44±8	41±9	0.368
Platelets, 10^9/L	349±148	331±124	0.624
White blood cell, 10^9/L	8.5±4	7.7±1.9	0.398
Total protein, g/L	15.5±3.6	17.6±5	0.743
Albumin, g/L	9.8±2.2	10.5±3	0.861
C-reactive protein, mg/L	18.8± 4	24.9±4.7	0.326
Lactate dehydrogenase, U/L	248.7±16.9	338.3±33.8	0.250
B-type natriuretic peptide, ng/L	860±204	3738±1384	0.003
Ferritin, ug/L	70.2±15.6	56.2±10.6	0.463
D-dimer, mg/L	0.87±0.21	1.97±0.82	0.236
Fib-4 index	0.69±0.4	1.6±0.22	0.003
Haemodynamic assessments			
RAP, mmHg	9.6±2.3	14.9±2.9	<0.001
mPAP, mmHg	29.3±4.3	39.5±6.9	<0.001
PAWP, mmHg	10.8±2.1	9.8±1.8	0.667
PVR, wood units	6.3±1.7	8.4±3.3	0.019
CI, l/min/m²	2.82±0.33	2.23±0.24	<0.001
Medication			
PDE-5 inhibitors, n (%)	32 (78%)	15 (85%)	0.581
ERAs, n (%)	27 (65%)	12 (60%)	0.482
Prostacyclin analogue, n (%)	8 (19%)	5 (25%)	0.596
Soluble guanylate cyclase stimulator, n (%)	6 (14%)	2 (10%)	0.856
Combination therapy, n (%)	35 (85%)	16 (80%)	0.085

BMI: Body mass index, WHO FC: World Health Organization Function Classification, 6MWD: Six min walk test distance, Fib-4: Fibrosis-4, RAP: Right atrial pressure, mPAP: Mean pulmonary artery pressure, PAWP: Pulmonary artery wedge pressure, PVR: Pulmonary vascular resistance, CI: Cardiac index, PDE-5: Phosphodiesterase type 5, ERAs: Endothelin receptor antagonists

Table 2. Univariate and multivariate analyses of mortality

Variables	Univariate analysis						Multivariate analysis					
	B	S.E.	WALD	P	OR	CI	B	S.E.	WALD	P	OR	CI
Fib-4 index	1.952	0.643	9.206	0.002	7.043	1.996-24.856	3.752	1.482	7.007	0.011	42.616	2.334-778.135
RAP	0.622	0.148	17.621	0.001	1.862	1.393-2.489	0.887	0.250	12.308	0.001	2.404	1.473-3.924
6MWD	1.444	0.234	6.943	0.001	0.843	0.416-0.753	1.621	0.383	7.057	0.001	1.014	1.013-1.210
Age	0.075	0.022	12.064	0.001	1.078	1.033-1.125						
BNP	0.011	0.042	8.675	0.003	1.001	1.013-1.029						
mPAP	0.262	0.065	16.503	0.001	1.300	1.145-1.475						
PVR	0.337	0.132	6.524	0.011	1.401	1.082-1.815						
CI	-6.137	1.521	16.283	0.001	0.002	0.017-0.043						

Fib-4: Fibrosis-4, RAP: Mean right atrial pressure, 6MWD: Six min walk test distance, BNP: B-type natriuretic peptid, mPAP: Mean pulmonary artery pressure, PVR: Pulmonary vascular resistance, CI: Cardiac index, CI: Confidence interval, OR: Odds ratio, S.E.: Standard error

No statistically significant disparities were observed among the remaining laboratory parameters. Upon analysis of the parameters of RHC conducted during the time of diagnosis, it was observed that the group of individuals who experienced mortality exhibited elevated values of RAP and mPAP compared with the non-mortality group (14.9±2.9 vs. 9.6±2.3, p≤0.001, 39.5±6.9 vs. 29.3±4.3, p≤0.001). The group of individuals who experienced mortality exhibited significantly elevated PVR values compared with the group that did not experience mortality (8.4±3.3 vs. 6.3±1.7, p=0.019). Additionally, the mortality group displayed lower CI values compared with the non-mortality group (2.23±0.24 vs. 2.82±0.33, p≤0.001). The data indicate a predominant use of pharmacotherapeutic interventions targeting PAH among the patient cohort, with a notable prevalence of combination therapy regimens. Among the cohort of surviving patients, 35 individuals accounting for 85% of the group, were undergoing combination therapy. Likewise, within the mortality group, it was noted that 16 individuals constituting 80% of the group, were also receiving combination therapy. Both cohorts exhibited comparable use of PAH-specific therapeutic interventions.

When the Fib-4 scores calculated from ALT, AST, and platelet values at the time of PAH diagnosis were compared in both groups, it was observed that the group with mortality had higher Fib-4 scores (1.6±0.22 versus 0.69±0.4, p=0.003). Independent predictors of mortality

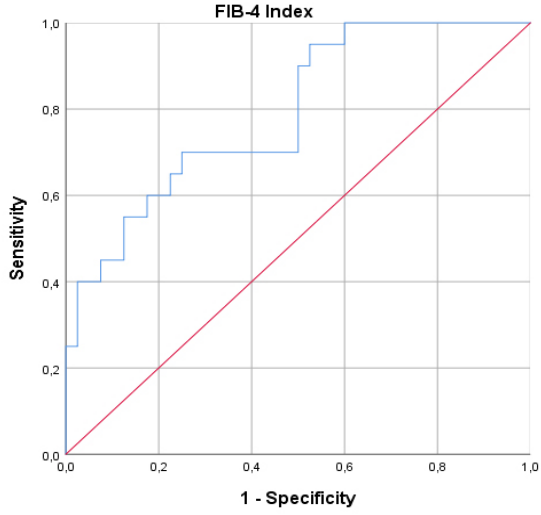

Figure 1. Receiver operating characteristic curve of Fib-4 index to predict mortality in PAH

PAH: Pulmonary arterial hypertension, Fib-4: Fibrosis-4

and the diagnostic performance of the Fib-4 index were analyzed by ROC curve analysis. Accordingly, the predictive value of the Fib-4 index for mortality was >1.02, with a sensitivity of 77% and specificity of 72% [AUC: 0.824, 95% confidence interval (CI): 0.740-0.880] (Figure 1).

Table 2 presents the results of the univariate and multivariate regression analyzes for mortality. In the univariate analysis, Fib-4 index, right atrial pressure, age,

6MWD, mPAP, PVR, CI, and BNP levels were predictive of mortality. Fib-4 index [hazard ratio (HR)=3.752, p=0.011, 95% CI=2.334-778.135], right atrial pressure (HR=0.887, p=0.001, 95% CI=1.473-3.924) and 6DYM (HR=1.621, p=0.001, 95% CI=1.013-1.210) were statistically significant variables in univariate analysis and were associated with increased mortality risk in multivariate regression analysis.

Discussion

Based on our current understanding, this investigation serves as the primary record concerning the prognostic implications of the Fib-4 index in patients diagnosed with PAH. The presence of an elevated Fib-4 index is significantly correlated with the mortality rates among patients diagnosed with PAH. Recent studies have acknowledged that PAH is a complex condition that affects multiple organs within the body. Anomalies have been documented in the systemic circulation, along with the central and peripheral nervous system, renal system, musculoskeletal system, and immune system[12,13]. The liver, which is in close anatomical and physiologic proximity to the right atrium (RA) and right ventricle (RV), is among the primary organs impacted by PAH-induced RV failure. The presence of RV volume and pressure overload can result in the development of congestive hepatopathy, which is often accompanied by various liver abnormalities.

To effectively monitor this particular medical condition and evaluate its prognosis, recent findings have indicated that noninvasive scoring systems exhibit superior capabilities in identifying patients with liver disorders compared with liver transaminases. In the present context, it is noteworthy to mention that the Fib-4 index has garnered significant attention as an extensively studied metric that exhibits a strong correlation with the identification of liver fibrosis through liver biopsy across various clinical scenarios. The aforementioned scenarios encompass the pathologies of viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease, as documented in the literature[14]. Previous investigations have elucidated the prognostic implications associated with compromised hepatic functionality in individuals with PAH[15].

In their comprehensive investigation, Divo et al.[16] conducted a meticulous examination to explore the existence of various comorbidities and their plausible impact on mortality risk among individuals afflicted with chronic obstructive pulmonary disease (COPD). While the incidence of liver cirrhosis is comparatively lower than that of cardiovascular and metabolic diseases, it is noteworthy that liver cirrhosis has been found to exhibit a substantial correlation with heightened mortality risk. In contrast, the present study exclusively recruited subjects exhibiting a less severe fibrotic load within the hepatic region, following the exclusion of individuals with pre-existing liver pathology. However, the advancement of mild or subclinical fibrosis within the hepatic system, as indicated by an elevated Fib-4 index, demonstrated an autonomous correlation with increased mortality rates. The aforementioned observation suggests that the presence of fibrotic burden within the liver could have a prognostic significance in patients diagnosed with PAH. Indeed, a recent longitudinal investigation has revealed that in patients with nonalcoholic fatty liver disease (NAFLD), both fatty liver and liver fibrosis exhibit independent associations with long-term overall mortality[17]. This finding is corroborated by Viglino et al.[18], who documented a notable tripling in the likelihood of initial cardiovascular incidents and mortality among individuals with COPD exhibiting liver fibrosis, in contrast to those lacking such fibrotic liver conditions. In a recent study, Fib-4 exhibited a significant correlation with heightened mortality risk in individuals diagnosed with coronary artery disease (CAD). This finding underscores the promising potential of Fib-4 as a prognostic biomarker in CAD[19].

Endothelin receptor antagonists (ERAs), such as bosentan, are used in the management of PAH. It is worth noting that ERAs have been linked to a relatively

infrequent yet noteworthy occurrence of liver enzyme elevations during treatment. These elevations are typically temporary and mild in nature; however, they may result in mild symptoms and necessitate adjustments in dosage or even discontinuation of the medication[20]. Certain ERAs have been linked to infrequent, yet potentially severe, instances of clinically noteworthy acute hepatic impairment[21]. Liver toxicity is a notable adverse reaction associated with bosentan therapy. A surveillance study revealed that approximately 7.6% of patients receiving bosentan exhibited increased levels of aminotransferases. In nearly half of these instances, the discontinuation of bosentan treatment was necessary because of the occurrence of drug-induced liver injury[22]. There is a potential correlation between elevated aminotransferase levels observed during ERA therapy and its impact on the Fib-4 index. Nevertheless, there was no significant difference between the ERA treatments used in both groups in our study.

In our investigation, the assessment of the RAP value through RHC revealed a significant prognostic association with mortality outcomes. Elevated RAP indicates RV overload in PAH and has been recognized as a well-established risk factor for mortality[23]. The size of RA has been identified as a significant prognostic indicator of adverse outcomes in PAH[24]. This finding is consistent with previous research that has also linked RA size to other cardiovascular conditions, including heart failure with reduced ejection fraction and right ventricular dysfunction[25]. In our investigation, the measurement of RAP through RHC was additionally discovered to possess prognostic value in predicting mortality outcomes. Nevertheless, the current understanding regarding the frequency and associated factors of RA dysfunction in PAH remains limited[26].

The 6-minute walk test, a widely employed assessment tool for gaging the physical exertion capabilities of individuals with PAH, holds significant clinical relevance as an indicator of overall mortality rates[27]. Multiple studies have substantiated the notion that a diminished 6MWD level is correlated with an escalated susceptibility to mortality, whereas an elevated 6MWD is linked to a diminished vulnerability to mortality[28,29]. Based on the most recent guidelines from the ESC and the ERS, a 6MWD result exceeding 440 m indicates a favorable prognosis. Conversely, a 6MWD result falling below 165 m is associated with an unfavorable prognosis[30]. In the present investigation, it was determined that the variable denoted as 6MWD exhibited independent prognostic significance about mortality.

Study Limitations

This study has certain limitations. First it is important to note that the methodology employed in our study is retrospective. Furthermore, this study encompassed a limited cohort of individuals and was conducted exclusively within a solitary medical facility. It is noteworthy that the dynamic fluctuations in hepatic functionality were not incorporated into the analysis, and further investigation is warranted to determine the transient or permanent nature of the observed abnormalities. In addition, it is worth noting that the analysis did not encompass prothrombin time and international normalized ratio, both of which serve as indicators of the liver's reserve function.

Conclusion

In summary, the Fib-4 index, RAP, and 6MWD have been identified as independent prognostic indicators in patients with PAH. Nevertheless, the Fib-4 index, a straightforward, cost-effective, and readily accessible tool, can be employed for predicting both the survival rates and the severity of the ailment in individuals suffering from PAH. Nevertheless, it is imperative to conduct extensive and comprehensive studies with a substantial sample size over an extended period of time to validate the findings and gain a deeper understanding of the intricate relationship and underlying mechanisms between hepatic function and PAH.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki on Human Research and approved by the Kahramanmaraş Sütçü İmam University Faculty of Medicine Ethics Committee (approval number: 01, date: 24.01.2023).

Informed Consent: Retrospective, single-center cohort study.

Peer-reviewed: Externally peer-reviewed.

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