Predictive Value of Liver Stiffness Using FIB-4 Index in Mortality of Heart Failure Patients (Philippine Heart Failure Registry)

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Abstract

BACKGROUND: Heart failure has an in-hospital mortality of 8.2% in the Philippines. The chronic passive congestion caused by heart failure is known to cause liver stiffness, which is proven using ultrasound elastography (US). However, US is not readily available in the Philippines; hence, a scoring system, the FIB-4 index, may have a prognostic value in patient with heart failure. This study aimed to establish the utility of the FIB-4 index as an independent risk factor of mortality in heart failure patients.

METHODS: This was a prospective study that included heart failure patients diagnosed using the Framingham criteria and enrolled in the Philippine Heart Failure Registry. FIB-4 index was computed for each patient and classified as having minimal FIB-4 index (<1.45); moderate (1.46 to 3.25) or advanced (>3.25). Regression analysis was performed to determine the association of FIB-4 index to mortality rate.

RESULTS: Of the 523 patients included in the study, majority were males (59.27%), newly diagnosed with heart failure (54.50%) and had no previous hospitalization (44.9%). Paroxysmal nocturnal dyspnea (82.41%) was the most common major criteria and dyspnea on exertion (88.10%) was the most common minor criteria present. Most complained of dyspnea (59%) on admission. The most common primary etiology of heart failure was hypertensive heart disease (30%). Regression analysis showed a five-fold increased risk of mortality (p=0.0001, 95% CI 2.1–11.7) in patient with FIB-4 index value >3.25, which increased to a 14-fold increase in risk after adjustment for covariates (p=0.0001, 95% CI 3.4–55.63), compared with patients with minimal to moderate FIB-4 index value.

CONCLUSION: Chronic passive congestion of the liver from heart failure leads to liver stiffness and those patients with advanced FIB-4 index value have a 14 times higher risk of mortality compared to those with minimal to moderate FIB-4 index value.

INTRODUCTION

Heart failure is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[1] These accompanying symptoms can include an elevated jugular venous pressure, pulmonary crackles and peripheral edema. The severity of the various symptoms of heart failure and exercise tolerance have been classically used to assess the severity of disease.[2,3] More recently, diagnostics markers such as N-terminal prohormone B natriuretic peptide have been used to identify patients with severe disease and poor prognosis.[4]

In search for other useful diagnostic tools for assessing patients with heart failure, studies in Japan were able to demonstrate that liver stiffness measured using elastography reflected heart failure severity and was a strong predictor for adverse events, including cardiac death and heart failure rehospitalization.[5-7]

Furthermore, the fibrosis-4 (FIB-4) index, a laboratory-based measure of liver research, was found to be useful for evaluating liver fibrosis or stiffness in patients with non-alcoholic fatty liver disease. Each parameters of the FIB-4 index (i.e., age, platelet count, alanine aminotransferase or ALT and aspartate aminotransferase or AST) can be easily measured in most centers.[7] A FIB-4 index <1.45 has a negative predictive value of >90% for advanced fibrosis of multiple etiologies whereas a score >3.25 has a positive predictive value of 65% and a specificity of 97% for advanced fibrosis.[9] With these findings, this study hypothesized that the FIB-4 index can serve as an important clinical tool to identify high-risk heart failure patients who may need more careful observation and more intensive treatment during hospital admissions.

Given the high burden of heart failure[7,8,10] and the need for accessible methods to assess and prognosticate these patients in the local setting, this study aimed to determine the utility of the FIB-4 index as an independent risk predictor of mortality among heart failure patients.

METHODS

This was a prospective observational study that included all heart failure patients, diagnosed with heart failure based on the Framingham criteria, and enrolled in the Philippine Heart Failure registry. All enrolled patients provided informed consent upon enrollment. Patients with chronic liver disease, chronic kidney disease on renal replacement therapy and cancer with metastasis to the liver were excluded.

The patient's age, sex, results of complete blood count, ALT and AST, history of heart failure diagnosis and previous hospitalization, chief complaint, etiology of heart failure, present components of the Framingham criteria and in-hospital outcomes were collected and tabulated. The FIB-4 index was calculated using the following formula: Age in years x AST in IU/L ÷ platelet count in 10^9 cells/L x square root of ALT in IU/L. Each patient was categorized into one of three groups based on their FIB-4 index: minimal (< 1.45), moderate (1.46 to 3.25) and advanced (>3.25). The correlation of FIB-4 index severity with in-hospital mortality was then determined using regression analysis.

RESULTS

A total of 523 patients were included in the study, more than half were males (59.27%) (Table 1). The mean age was 55.86 ± 16.59 years (range 21 to 88 years). The most common chief complaint was dyspnea (59.50%), followed by edema (38.20%) and fatigue (30.80%). Hypertensive heart disease was the most common cause of heart failure (30.2%) (Table 2). The most common major Framingham criteria present were paroxysmal nocturnal dyspnea (82%), followed by rales (59%) and neck vein distention (40.90%) (Table 3). For minor criteria, the most common were dyspnea on exertion (88.70%), followed by ankle edema (52.80%) and night cough (18.40%).

Table 1. Baseline characteristics of included patients

Characteristic	No. (n = 523)	%
Sex		
Male	310	59.3
Female	213	40.7
Age (years)		
Mean +/- SD	55.9 +/- 15.6	
Range	21 – 88	
Prior hospitalization		
Never	235	44.9
1-2 times	201	38.4
>2 times	81	15.5
No data	6	1.1
History of heart failure diagnosis		
Newly diagnosed	285	54.5
Previously diagnosed	235	44.9
No data	3	0.6
Chief complaint		
Dyspnea	311	59.5
Edema	200	38.2
Fatigue	161	30.8
Orthopnea	154	29.4
Angina	101	19.3
Paroxysmal nocturnal dyspnea	40	7.6
Palpitations	25	4.8
Nausea	20	3.8
Syncope	3	0.6
Cardiac arrest	2	0.4
Near-syncope	1	0.2
Others	58	11.1

Table 2. Etiology of heart failure

Etiology	No. (N=523)	%
Hypertensive heart disease	158	30.2
Acute coronary syndrome	114	21.8
Coronary artery disease (undiagnosed)	108	20.7
Coronary artery disease (diagnosed)	81	15.5
Valvular rheumatic heart disease	79	15.1
Valvular non-rheumatic heart disease	39	7.5
Thyroid disease	24	4.6
Cardiomyopathy	23	4.4
Idiopathic/unknown	15	2.9
Congenital	12	2.3
Toxins/drugs	11	2.1
Infectious	10	1.9
Pericardial Disease	7	1.3
Others	14	2.7
Anemia	11	2.1
Acute atrial fibrillation	2	0.4
Chronic obstructive pulmonary disease	1	0.2

Table 3. Components of the Framingham Criteria fulfilled

	No. (n=523)	%
Major Criteria		
Paroxysmal nocturnal dyspnea	431	82.4
Rales	312	59.7
Neck vein distention	214	40.9
Cardiomegaly	199	38.0
Pulmonary edema	86	16.4
S3 gallop	62	11.9
Hepatojugular reflux	14	2.7
Venous pressure	1	0.2
Minor Criteria		
Dyspnea on exertion	464	88.7
Ankle edema	276	52.8
Night cough	96	18.4
Pleural effusion	93	17.8
Heart rate >120 beats per minute	75	14.3
Weight loss >4.5kg in 5 days	56	10.7
Hepatomegaly	21	4.0
Vital capacity	1	0.2

Table 4. Distribution of heart failure patients by FIB-4 index severity

FIB-4 index severity	Patients (n,%)	Mortality (n,%)
Minimal	255 (48.8)	8 (3.1)
Moderate	169 (32.3)	1 (0.6)
Advanced	99 (18.9)	8 (8.1)

Table 5. Crude and adjusted risk of mortality of advanced vs minimal FIB-4 Index

FIB-4	Odds ratio (Advanced vs minimal)	95% CI	p-value
Crude	5.00	2.13–11.70	<0.0001
Adjusted*	13.79	3.42–55.63	<0.0001

**Controlled for the effects of sex, prior hospitalization, history of heart failure, primary etiology, pre-hospitalization comorbidities, smoking, alcohol, edema, crackles and precipitating factors.*

The mean computed FIB-4 index was 2.3 ± 2.9 (range 0.2 to 19.1). Majority of heart failure patients had minimal (48.8%) or moderate (32.3%) FIB-4 index (Table 4). Regression analysis showed a five-fold increased risk of mortality (OR 5.00; p<0.0001) in patients with advanced FIB-4 index compared to those with minimal FIB-4 index (Table 5). After adjustment, the OR increased to 13.79 (p<0.0001).

DISCUSSION

Heart failure is a progressive disorder characterized by the loss of functioning myocytes or disruption of the myocardium, leading to inadequate force generation during contraction. The decline in the pumping ability of the myocardium and the resulting left ventricular dysfunction eventually lead to backflow and congestion of blood and fluids in other organs. The markedly increased pressure in the right side of the heart leads to dilatation of the inferior vena cava and hepatic veins, hepatomegaly and increased liver stiffness, which has been used as a marker of cardiac status.[11]

A small study of 30 patients (70% males; mean age of 42.2 ± 13.3 years) who underwent left ventricular assist device implantation measured liver stiffness preoperatively using FibroScan. The study found that the mean preoperative liver stiffness was 13.3 ± 13.0 kPa compared to the normal liver stiffness of <5.5 kPa; liver stiffness was abnormal in 77% of patients.[11] The outcome of patients correlated with liver stiffness. Four patients also required right ventricular assist device (RVAD), and the liver stiffness of these patients tended to be higher than those who did not require RVAD. Furthermore, no patient with liver stiffness ≤7.0 kPa required RVAD. The incidence of major adverse events was lower in those with liver stiffness ≤12.5 kPa (25% vs. 80%; p<0.05) and there were no deaths in these patients.

One limitation of the FibroScan is its low availability in the Philippines. Hence, an alternative marker using readily accessible diagnostic tests may be beneficial. During liver congestion, the liver releases serum bilirubin, alkaline phosphatase, gamma-glutamyl transferase, AST and ALT. The latter two are integral factors for computing the FIB-4 index, together with age and platelet count. This study also showed that the FIB-4 index is predictive of mortality in patients with heart failure.

A similar study conducted in Japan also reported the prognostic value of the FIB-4 index. The study included 1,058 patients with heart failure, who were then categorized into tertiles of FIB-4: FIB-4 index <1.72 (n=353); 1.72≤ FIB-4 index <3.01 (n=353) and FIB-4 index ≥ 3.01 (n=352). After a follow-up of almost three years, all-cause mortality progressively increased from the first to third groups (12.2%, 21.0% and 36.6%, respectively; p<0.01).[7] Cox proportional hazard analysis showed that FIB-4 index was an independent predictor of all-cause mortality in patients with heart failure (p<0.05). Those in the highest tertiles also had higher left atrial volume, mitral valve E/e', inferior vena cava diameter and right atrial end-systolic area (p<0.01 for all). Given the strong correlation between the FIB-4 index and mortality demonstrated in the present study, the index may be used as a fast and readily available diagnostic score to easily assess the severity of heart failure, especially in settings where sophisticated diagnostic tools such as ultrasound elastography are lacking.

However, this study has a number of limitations. The study was limited to in-hospital patients. The researchers did not classify patients based on the systolic function (heart failure with preserved vs reduced ejection fraction). Finally, interventions that may affect patient outcomes were not taken into account. Inclusion of out-patients, stratification of patients by systolic function and inclusion of interventions used in patient management, whether invasive or non-invasive, may be considered in future studies and analyses of the Philippine Heart Failure registry data.

CONCLUSION

The FIB-4 index is a simple and inexpensive method that correlates well with in-hospital mortality rate. It may be used as a scoring system to stratify the risk of in-hospital mortality among heart failure patients.

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