The Correlation Between Fibrosis-5 Index (Fib-5) and Fibrosis-4 Index (Fib-4) with the Duration of Heart Failure

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Article

The Correlation Between Fibrosis-5 Index (Fib-5) and Fibrosis-4 Index (Fib-4) with the Duration of Heart Failure

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Abstract: Aim: This study aimed to explore the correlation between the FIB-5 and FIB-4 indices, which assess liver fibrosis, and the grouped duration of heart failure (HF) in a cohort of subjects from the National Health and Nutrition Examination Survey (NHANES) 2015-2020. **Methods**: The study included 468 participants categorized into three groups based on HF duration: Group 1 (≤1 year, n=91), Group 2 (1-5 years, n=87), and Group 3 (>5 years, n=290). Data were analyzed using Pearson and Spearman correlation analyses to assess relationships between FIB-5, FIB-4, and HF duration. Clinical variables such as age, BMI, ALT, AST, albumin, and platelet count were also considered. **Results**: The analysis revealed significant correlation between FIB-5 with age (Pearson correlation (r) = -0.29, $p<0.0001$) but not for HF duration across groups (Spearman correlation (ϱ) = -0.010, p=0.8217). The FIB-4 index did not show significant associations with the HF duration group (p=0.6326). The regression analysis also showed no significant predictive relationship between FIB-5 or FIB-4 and the duration of heart failure, further supporting the lack of association between fibrosis indices and HF duration in this cohort. **Conclusion**: The study found no significant correlation between the FIB-5 and FIB-4 indices and the duration of heart failure in this cohort. These findings suggest that while these fibrosis scores are useful in liver assessment, they may not directly reflect the duration of heart failure in this population. Further studies are needed to explore other potential biomarkers for HF duration.

Keywords: Liver fibrosis Biomarker; Duration of disease; cardiovascular health; cardiac dysfunction; Prognosis

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Introduction

Heart failure (HF) is a complex syndrome characterized by the heart's inability to pump blood effectively, resulting in insufficient delivery of oxygen and nutrients to the body's tissues. This condition is a leading cause of morbidity and mortality worldwide, with a steadily increasing prevalence due to an aging population and improved survival rates for cardiovascular diseases. Despite advancements in therapeutic strategies, the prognosis of HF patients remains poor, with high rates of hospitalization, recurrent exacerbations, and mortality. Accurate prognostication is critical for effective management and resource allocation in HF care, as traditional prognostic markers such as the New York Heart Association (NYHA) functional class and left ventricular ejection fraction (LVEF) often fail to predict outcomes across the spectrum of the disease[1-3].

In recent years, biomarkers have gained attention for their potential to enhance risk stratification in HF[4]. Biomarkers are measurable indicators that can reflect disease processes or responses to treatments, offering a more precise and individualized approach to patient care. While cardiac-specific biomarkers have been widely studied, there is increasing recognition of the liver's role in HF pathophysiology. Liver dysfunction is common in HF patients, often resulting from passive congestion due to elevated right-sided pressures and reduced perfusion caused by low cardiac output. This dual insult can lead to liver injury and fibrosis, which are important factors in disease progression and prognosis [4-6].

Among the liver-related biomarkers, indices such as Fibrosis-4 (FIB-4) and Fibrosis-5 (FIB-5) have emerged as useful tools for assessing liver fibrosis in various clinical settings. These non-invasive scoring systems combine clinical parameters, such as liver enzymes and platelet count, to estimate the degree of fibrosis [7]. While studies have highlighted the prognostic value of liver fibrosis indices in HF, the specific role of FIB-5 in HF outcomes remains underexplored. Understanding the relationship between liver fibrosis and HF may provide new insights into the pathophysiology of the disease and improve the management of HF patients. This study aims to explore the correlation between the FIB-5 index, FIB-4, and the duration of heart failure, further investigating the potential utility of these indices in refining HF prognosis.

Methods and Material

Data Source and Study Population

The data for this study was sourced from the National Health and Nutrition Examination Survey (NHANES) 2015-2020, which is managed by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention (CDC). NHANES is an ongoing, cross-sectional study designed to assess the health and nutritional status of the U.S. population. It offers extensive, representative data on demographics, physical assessments, laboratory results, and survey responses, ensuring unbiased and comprehensive insights.

Subjects' Data Collection

Data for this analysis was gathered through questionnaires, laboratory testing, and physical exams. The study examined a range of factors, including age, gender, body mass index (BMI), liver enzymes (alanine aminotransferase (ALT) and aspartate aminotransferase (AST)), high-density lipoprotein (HDL), serum glucose, platelet count (PLT), and hemoglobin A1c (HbA1c).

Biomarkers

FIB-4 is a non-invasive scoring tool used to estimate liver fibrosis, incorporating age, AST, ALT, and platelet count. The formula for FIB-4 is as follows: $FIB\text{-}4 = (Age\ (years) \times AST\ (U/L)) / (Platelet\ count\ (10^9/L) \times \sqrt{ALT\ (U/L)})$.

The FIB-5 score, another marker of liver fibrosis, incorporates albumin, alkaline phosphatase (ALP), AST, ALT, and platelet count. The FIB-5 formula is: $FIB\text{-}5 = \{(Albumin\ (g/L) \times 0.3) + (Platelet\ count\ (10^9/L) \times 0.05)\} - \{(ALP\ (U/L) \times 0.014) + (AST/ALT\ Ratio \times 6) + 14\}$.

Grouping

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Subjects were divided into three groups based on the duration of HF. Group 1 represents individuals with HF for one year or less, Group 2 includes those with HF lasting from one to five years, and Group 3 comprises individuals with HF for over five years.

Statistical Analysis

For statistical analysis, Qualitative variables were summarized as frequencies, while continuous variables were expressed as either mean ± standard deviation (SD) or median (range), depending on the data distribution. The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. For comparisons between groups, one-way ANOVA was applied for normally distributed data, and the Kruskal-Wallis test was used for non-normally distributed data. The Chi-square test was employed to assess associations between categorical variables. Additionally, linear regression was performed to evaluate relationships between continuous variables, and Pearson's and Spearman's correlation coefficient were used to assess the strength and direction of the monotonic relationships between variables. All statistical tests were conducted using GraphPad Prism 8. Significance level considered as $P < 0.05$ for all tests.

Results

Descriptive Analysis

A total of 468 subjects with previously diagnosed HF were included in the analysis. The participants were categorized into different groups based on the presence or absence of key characteristics, such as gender, hypertension history, and diabetes mellitus history, as well as the duration of HF. The following sections present the descriptive statistics for categorical and continuous variables.

Among the total of 468 subjects, 193 were female (41.3%), and 275 were male (58.7%), which reflects the gender distribution within the sample. A large portion of the cohort (383, or 81.9%) had a history of hypertension, and 245 subjects (52.4%) had a history of diabetes. The median age of heart failure onset was 58 years, with a mean of 56.51 years. The median values for FIB-4 and FIB-5 were 1.61 and 0.17, respectively, with means of 1.79 and 0.12 (**Table 1**).

Table 1. Descriptive Statistics for Continuous Variables. This table presents the descriptive statistics for continuous variables, such as age, BMI, and several biochemical parameters, for the entire study cohort.

	Total number of values	Median	Mean	Std. Deviation	Std. Error of Mean
Age	468	69	66.71	11.80	0.55
Age of HF	468	58	56.51	15.13	0.70
BMI	451	31.4	32.89	8.60	0.41
ALT	468	18	20.73	16.66	0.77
AST	468	21	24.61	38.74	1.79
ALB (g/l)	468	40	39.66	4.02	0.19
ALP	468	77	83.78	33.07	1.53
BUN (mmol/L)	468	6.43	7.41	3.87	0.18
Cr (umol/L)	468	92.82	110.18	89.77	4.15
Globulin (g/L)	468	31	31.19	5.80	0.27
Glucose (mmol/L)	468	5.66	6.83	3.31	0.15
GGT (IU/L)	468	24	40.94	59.38	2.74
PLT	468	211	220.29	63.83	2.95
Chol (mmol/l)	468	4.16	4.39	1.13	0.05
HDL (mmol/l)	468	1.24	1.30	0.44	0.02
HbA1c	468	6	6.47	1.47	0.07

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FIB-5*	468	0.17	0.12	4.58	0.21
FIB-4	468	1.62	1.79	1.05	0.05
* minimum: -23.98, Maximum: 11.12					

Subgroup Descriptive Analysis

The study included a total of 468 subjects, all diagnosed with HF, categorized into three distinct groups based on the duration of their HF. Group 1, consisting of 91 subjects, represents the earliest stage of HF with 1 or under 1 year of HF, while Group 2 (87 subjects) reflects a more intermediate stage with 1 to 5 years of HF, and Group 3 (290 subjects) encompasses those with a longer duration of HF (five or over five years of HF).

The gender composition varied across the groups, with Group 1 having a near-equal split (49 females and 42 males), indicating a relatively balanced representation. However, as the condition progressed in Groups 2 and 3, the male population significantly increased. Group 2 had 34 females and 53 males, while Group 3, the largest group, consisted of 110 females and 180 males ($P = 0.0244$). This shift could reflect the increasing prevalence of HF in older males, a trend observed in many heart disease studies.

Hypertension was common across all groups. In Group 1, 74 subjects had a history of hypertension, while 15 did not. Group 2 also showed a high prevalence, with 74 subjects reporting hypertension and only 13 without it. However, the prevalence of HTN dramatically increased in Group 3, where 235 subjects had a history of the condition, and 55 did not. This progression underscores the role of chronic hypertension as a key contributor to the development and exacerbation of heart failure. The difference between the history of hypertension in groups was not significant ($P = 0.6881$).

The prevalence of diabetes also varied across the groups. In Group 1, 31 subjects were diagnosed with diabetes, and 57 were not, with an additional 3 subjects categorized as borderline. Group 2 displayed a similar pattern, with 35 subjects having diabetes, 46 without, and 6 being borderline. Interestingly, Group 3 exhibited the highest number of diabetic subjects, with 136 reporting a diabetes diagnosis, while 142 were not diabetic. Additionally, 12 subjects in Group 3 were borderline for diabetes. This increase in diabetes prevalence as heart failure duration extends aligns with established research that shows a close relationship between diabetes and worsening heart failure. The difference between the history of diabetes in groups was not significant ($P = 0.0816$).

Table 2 provides the descriptive statistics (mean ± standard deviation) for various demographic and laboratory measures across all three groups.

Table 2. Descriptive statistics (mean ± standard deviation) of laboratory measures across three groups. Kruskal-Wallis test had been used.

Variable	*Group 1 (N=91)*	*Group 2 (N=87)*	*Group 3 (N=290)*	*P-value*
Age	70.30 ± 12.23	63.62 ± 11.85	66.51 ± 11.39	<0.0001*
Age of HF diagnosis	69.96 ± 12.43	60.66 ± 11.88	51.06 ± 13.71	<0.0001*
BMI (kg/m²)	31.77 ± 8.25	33.00 ± 9.85	33.19 ± 8.32	0.2546
ALT (IU/L)	22.92 ± 29.09	21.14 ± 17.26	19.92 ± 9.70	0.3130
AST (IU/L)	32.09 ± 85.47	21.85 ± 11.54	23.10 ± 9.41	0.0582
ALB (g/L)	39.96 ± 3.71	38.48 ± 4.71	39.92 ± 3.84	0.0247*
ALP (IU/L)	85.34 ± 37.92	88.03 ± 39.59	82.01 ± 29.05	0.5290
BUN (mmol/L)	7.66 ± 3.17	7.94 ± 4.82	7.17 ± 3.73	0.1234
Cr (umol/L)	105.69 ± 63.41	139.96 ± 155.79	102.66 ± 64.94	0.1457
Globulin (g/L)	30.78 ± 6.58	31.47 ± 5.20	31.24 ± 5.72	0.3852
Glucose (mmol/L)	6.56 ± 2.98	6.87 ± 3.56	6.90 ± 3.34	0.7648
GGT (IU/L)	41.51 ± 57.17	40.64 ± 48.98	40.85 ± 62.97	0.8867
PLT (x10^9/L)	224.20 ± 63.90	222.89 ± 66.38	218.29 ± 63.16	0.6470
Cholesterol (mmol/L)	4.56 ± 1.30	4.37 ± 1.05	4.34 ± 1.09	0.5696

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HDL (mmol/L)	1.43 ± 0.50	1.19 ± 0.41	1.27 ± 0.41	0.0068*
HbA1c (%)	6.30 ± 1.27	6.40 ± 1.39	6.54 ± 1.54	0.2349
FIB-5	0.35 ± 4.84	-0.02 ± 5.14	0.09 ± 4.33	0.086
FIB-4	1.99 ± 1.43	1.57 ± 0.78	1.80 ± 0.97	0.0403*

Comparative Analysis

For the FIB-5 analysis, tests for homogeneity of variances revealed non-significant differences in variance across the groups. The Brown-Forsythe test yielded a P-value of 0.0801, indicating near-homogeneous variances. Similarly, Bartlett's test indicated no significant differences in variances (χ^2 = 4.8, P = 0.0918). These results suggest that the variances among groups are not significantly different (P > 0.05). However, the Kolmogorov-Smirnov test revealed a P-value of 0.0126 for FIB-5, indicating that the data does not follow a normal distribution. This violation of normality assumptions necessitated consideration of non-parametric methods.

For FIB-4, Bartlett's test revealed significant differences in variances (P < 0.0001), confirming heteroscedasticity. Given the combination of non-normality for FIB-5 and variance inequality for FIB-4, the Kruskal-Wallis test was deemed appropriate for analyzing these biomarkers.

This test was conducted to compare FIB-5 values among the three groups based on the duration of heart failure diagnosis. The analysis showed no statistically significant difference in the medians of the FIB-5 scores across the groups (P = 0.086). This indicates that the duration of heart failure diagnosis (categorized into less than 1 year, 1–5 years, and more than 5 years) did not result in significant variability in FIB-5 scores. The data included 468 total observations distributed across the three groups, with no significant median differences detected at (P < 0.05).

In contrast, this test for FIB-4 revealed a statistically significant difference in medians among the three groups (P = 0.0403), suggesting that the duration of heart failure diagnosis may influence FIB-4 scores.

Correlation Study

The correlation analysis conducted on all subjects revealed significant correlations between FIB-5 and various variables. Specifically, significant relationship was found between FIB-5 and age (Pearson correlation (r) = -0.29, p <0.0001), or between FIB-5 and age of HF onset (r = -0.20, p <0.0001). In contrast, the correlation between FIB-5 the duration of HF (1: 1 year, 2: 1-5 years, 3: 5 years) was also non-significant (Spearman correlation (ϱ) = -0.010, p = 0.8217) (**Table 3**).

The correlation between FIB-4 and the duration of HF showed no significant result (ϱ = 0.022, p = 0.6326). It is important to note that the correlation between FIB-4 and age was excluded from this analysis because age is part of the FIB-4 formula itself, which may lead to a spurious correlation if considered.

Table 3. The correlation analysis between FIB-4 and FIB-5 with other parameters.

	Correlation	*95% confidence interval*	*R squared*	*P value*	*P value summary*
(Pearson) *FIB-5 vs. Age*	-0.29	-0.37 to -0.21	0.086	<0.0001	****
(Pearson) *FIB-5 vs. Age of HF*	-0.20	-0.29 to -0.11	0.041	<0.0001	****
(Spearman) *FIB-5 vs. HF onset group*	-0.010	-0.10 to 0.083	N/A	0.8217	ns

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(Spearman) *FIB-4 vs. HF onset group*	0.022	-0.071 to 0.12	N/A	0.6326	ns

FIB-5 and Duration of Heart Failure

A multivariable linear regression analysis was performed to assess the association between clinical and demographic variables and the FIB-5 score. The overall model was statistically significant (P = 0.0011), with an R^2 value of 0.098, indicating that the model explained 9.8% of the variance in FIB-5 scores.

Among the included variables, **age** (β = −0.1139, P <0.0001) showed statistically significant associations with FIB-5 (**Table 4**). Other variables, including gender, BMI, HbA1c, duration of heart failure, history of hypertension, and history of diabetes, were not significantly associated with FIB-5 scores (P >0.05).

So, gender, BMI, and HbA1c were identified as significant predictors of FIB-5 in this cohort, while the overall explanatory power of the model was limited.

Table 4. Multivariable Linear Regression Analysis for FIB-5.

Variable	*Estimate (β)*	*Standard Error*	*95% Confidence Interval*	*P-value*	*Significance*
Gender	-0.01985	0.4329	-0.8706 to 0.8309	0.9634	ns
Age	-0.1139	0.01820	-0.1497 to -0.07816	<0.0001	****
Duration of Heart Failure	-0.3756	0.2675	-0.9014 to 0.1502	0.1611	ns
BMI	0.01996	0.02585	-0.03084 to 0.07077	0.4404	ns
History of Hypertension	-0.03852	0.3206	-0.6685 to 0.5915	0.9044	ns
History of Diabetes	-0.04191	0.3166	-0.6641 to 0.5803	0.8947	ns
HbA1c	0.2791	0.1519	-0.01945 to 0.5776	0.0668	ns

Notes:
ns*: Not significant (P>0.05)*
***: Significant at P<0.05*
β: Regression coefficient indicates the effect size and direction of each variable on FIB-5.

FIB-4 and Duration of Heart Failure

A multivariable linear regression analysis was conducted to evaluate the associations between clinical and demographic variables and the FIB-4 score. The model was statistically significant (P<0.0001) with an R^2 value of 0.1655, indicating that the model accounted for 16.55% of the variance in FIB-4 scores.

Among the evaluated variables, **HbA1c** (β = −0.0869, P = 0.01) was significant predictors of FIB-4 scores (**Table 5**). HbA1c showed an inverse relationship with FIB-4, with a 0.087-unit decrease per unit increase in HbA1c. Other variables, including gender, duration of heart failure, BMI, and history of hypertension and diabetes, were not significantly associated with FIB-4 (P >0.05).

The findings demonstrate that HbA1c are key predictors of FIB-4 in this cohort, with the model explaining a modest proportion of the variance.

Table 5. Multivariable Linear Regression Analysis for FIB-4.

Variable	*Estimate (β)*	*Standard Error*	*95% Confidence Interval*	*P-value*	*Significance*
Gender	0.0667	0.0957	-0.1214 to 0.2548	0.4862	ns
Duration of Heart Failure	-0.0094	0.0592	-0.1257 to 0.1068	0.8734	ns

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BMI	-0.0067	0.0057	-0.0179 to 0.0046	0.2445	ns
History of Hypertension	-0.0249	0.0709	-0.1642 to 0.1144	0.7259	ns
History of Diabetes	0.0732	0.0700	-0.0644 to 0.2108	0.2963	ns
HbA1c	-0.0869	0.0336	-0.1529 to -0.0209	0.0100	*

Notes:

***ns**: Not significant (P>0.05)*

***: Significant at P<0.05*

β: Regression coefficient indicates the effect size and direction of each variable on FIB-5.

Discussion

The prognosis of HF remains a significant focus in cardiovascular research due to its increasing prevalence and associated morbidity and mortality [1, 2]. Biomarkers, particularly liver-related indices such as FIB-4 and FIB-5, have emerged as promising tools for improving prognostic evaluation in HF [4, 8, 9]. This study investigated the relationship between these biomarkers and the duration of HF, alongside their potential roles in stratifying risk in patients with HF. The results provide valuable insights, though some findings challenge conventional expectations about the association between liver fibrosis markers and HF progression.

This study aimed to explore various demographic, clinical, and laboratory predictors associated with two liver fibrosis indices, FIB-5 and FIB-4, in a cohort of patients diagnosed with HF. The cohort comprised 468 subjects, with a notable gender disparity (41.3% females and 58.7% males) and a predominant history of hypertension (81.9%) and diabetes mellitus (52.4%). The descriptive analysis revealed that the majority of participants had a longer duration of HF, as evidenced by the large group of subjects in the third category (those with HF duration greater than five years).

One of the key observations from this study was the shift in gender distribution across the duration of heart failure groups. The data revealed a near-equal gender distribution in the early stages of HF (Group 1), but as the disease progressed (Groups 2 and 3), the proportion of males significantly increased. This trend aligns with findings from previous studies, which suggest that HF is more prevalent in older males, possibly due to the cumulative effects of comorbid conditions such as hypertension, coronary artery disease, and diabetes that are more common in men as they age.

This underscores the role of hypertension as a key contributor to the initiation and progression of HF. However, despite the increasing prevalence of hypertension with HF duration, the statistical analysis revealed no significant differences between the groups, indicating that hypertension is uniformly prevalent across different stages of HF.

Similarly, diabetes prevalence was highest in the longest-duration HF group (Group 3), with 136 subjects diagnosed, further supporting the association between diabetes and worsening heart failure. While the data showed a trend in increasing diabetes prevalence with longer HF duration, the difference between the groups was not statistically significant, suggesting that while diabetes may play a role in worsening HF, it does not exhibit a marked differentiation across disease stages.

In terms of liver fibrosis scores, FIB-5 and FIB-4 were both assessed to understand their relationship with heart failure duration and other clinical factors. While the FIB-5 score did not significantly vary across the duration-based groups, the FIB-4 score exhibited significant differences, suggesting that the duration of HF might influence liver fibrosis as measured by FIB-4. However, the exact clinical implications of these findings remain unclear and require further exploration.

FIB-4, on the other hand, demonstrated a significant relationship with HF duration. Patients with longer HF duration exhibited higher median FIB-4 scores, potentially reflecting the cumulative impact of systemic stress and hepatic dysfunction over time. These findings support prior studies linking FIB-4 to cardiovascular outcomes, including its role as a predictor of HF-related rehospitalization and mortality [10-12].

While the study demonstrated no direct correlation between FIB-5 and HF duration, its prognostic utility in predicting adverse outcomes remains well-supported [7, 13]. The ability of FIB-5 to identify patients at higher risk of rehospitalization or mortality, particularly when combined with

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inflammatory markers like CRP, reinforces its value in risk stratification [14]. However, its lack of sensitivity to HF chronicity may limit its role in tracking disease progression.

The prognostic capabilities of FIB-5 and FIB-4 extend beyond HF duration. Lower FIB-5 scores are independently associated with higher rates of adverse outcomes, including rehospitalization and mortality, even after adjusting for confounders like left ventricular ejection fraction (LVEF) [7]. The synergistic use of FIB-5 with inflammatory markers like C-reactive protein (CRP) further enhances risk stratification. In one study, patients with both low FIB-5 and high CRP levels experienced significantly worse outcomes, with a hazard ratio (HR) of 1.67 for major adverse cardiac and cerebrovascular events (MACCEs) [14]. This dual-marker approach improved predictive metrics ($P < 0.001$), underscoring the interplay between systemic inflammation and hepatic dysfunction in HF [14].

In contrast, FIB-4 has demonstrated utility in predicting cardiovascular outcomes in specific HF subtypes. For instance, advanced fibrosis identified by FIB-4 (>2.67) is associated with higher rehospitalization rates in HFpEF patients ($P < 0.001$) [10, 15]. Additionally, FIB-4 predicts mortality and hospitalization risk in various cardiovascular contexts, including right ventricular pacing and myocardial infarction [16-18]. Despite these promising findings, FIB-4's prognostic value appears less robust after multivariable adjustment, particularly in HFpEF populations [12, 15].

The correlation analysis showed that FIB-5 correlated significantly with age and the age of heart failure onset, but not the duration of HF. This suggests that these liver fibrosis indices might be directly influenced by the demographic factors examined but not HF duration, raising questions about the potential utility of these scores as general markers for disease progression in heart failure patients.

Multivariable linear regression analyses provided more insight into the predictors of FIB-5 and FIB-4 scores. For FIB-5, significant predictor was age. Notably, HbA1c had no significant relationship with FIB-5. This result is somewhat counterintuitive, as one might expect that worse metabolic control would not correlate with more severe liver damage. However, this finding could reflect the complexity of the interplay between metabolic factors and liver fibrosis in heart failure patients, warranting further investigation.

Descriptive analyses highlighted the clinical characteristics of the cohort. The median age of heart failure onset was 58 years, with mean FIB-4 and FIB-5 values of 1.79 and 0.17, respectively. The multivariable linear regression analysis revealed that age was significant predictor of FIB-5 scores ($P < 0.0001$), while only HbA1c significantly influenced FIB-4 scores ($P = 0.01$). These findings suggest that while liver fibrosis indices are influenced by demographic and metabolic factors, their prognostic role in HF extends beyond these variables.

In contrast, the analysis of FIB-4 scores revealed that HbA1c was the only significant predictor. An increase in HbA1c was associated with a decrease in FIB-4 scores, which might point to a complex relationship between diabetes management and liver fibrosis. Interestingly, the duration of HF, history of hypertension, and other demographic factors were not significantly associated with FIB-4, suggesting that liver fibrosis, as measured by FIB-4, might be more sensitive to glycemic control rather than the duration or severity of heart failure.

While this study provides valuable insights into the associations between liver fibrosis indices and demographic and clinical factors in heart failure patients, several limitations must be acknowledged. First, the observational nature of the study limits the ability to establish causal relationships. The sample was also predominantly composed of individuals with chronic HF, and the findings might not apply to those in earlier or more acute stages of the disease. Additionally, while HbA1c was a significant predictor for FIB-4, the study did not explore the underlying mechanisms linking glycemic control to liver fibrosis in depth. Future studies should aim to investigate these relationships in more detail and assess the potential role of liver fibrosis in predicting clinical outcomes in HF patients.

Conclusions

In conclusion, this study demonstrates that both FIB-5 and FIB-4 indices, while reflective of liver fibrosis, do not show significant correlations with the duration of HF. Although previous research suggests potential relationships between liver fibrosis and cardiovascular conditions, our findings indicate that the duration of HF does not directly influence these fibrosis scores. These results highlight the need for further investigation into the complex interplay between liver function and heart failure progression.

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Conflicts of Interest: The author declare that they have no conflict of interest.

Data Availability: Data is available at the official website of NHANES (https://www.cdc.gov/nchs/nhanes/index.htm).

Ethical approval: The studies involving human participants were reviewed and approved by the Centers for Disease Control and Prevention. The participants provided their written informed consent to participate in this study. The NHANES database was approved by the Ethics Review Committee of the National Center for Health Statistics (Protocol #2018-01 (Effective beginning October 26, 2017), Continuation of Protocol #2011-17 (Effective through October 26, 2017)).

Animal Studies: Not applicable.

Research involving recombinant DNA: Not applicable.

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Authors' Contributions: MS: Reviewing the literature, Methodology, Investigation, Conceptualization, Data curation, Formal analysis, Writing – the original draft, review & and editing.

References

1. Sotoudeheian M, Hoseini S. Understanding the Pathophysiology of Heart Failure with Mid-Range Ejection Fraction: A Comprehensive Narrative Review. 2023.
2. Sotoudeheian MJ, Mirahmadi S-M-S, Pirhayati M, Azarbad R, Nematollahi S, Taghizadeh M, et al. Understanding the Role of Galectin-1 in Heart Failure: A Comprehensive Narrative Review. Current Cardiology Reviews. 2024;20:82-90.
3. Rohde LE, Zimerman A, Vaduganathan M, Claggett BL, Packer M, Desai AS, et al. Associations between New York Heart Association classification, objective measures, and long-term prognosis in mild heart failure: a secondary analysis of the PARADIGM-HF trial. JAMA cardiology. 2023;8:150-8.
4. Sarhene M, Wang Y, Wei J, Huang Y, Li M, Li L, et al. Biomarkers in heart failure: the past, current and future. Heart failure reviews. 2019;24:867-903.
5. Savic-Radojevic A, Pljesa-Ercegovac M, Matic M, Simic D, Radovanovic S, Simic T. Novel biomarkers of heart failure. Advances in clinical chemistry. 2017;79:93-152.
6. Passino C, Barison A, Vergaro G, Gabutti A, Borrelli C, Emdin M, et al. Markers of fibrosis, inflammation, and remodeling pathways in heart failure. Clinica Chimica Acta. 2015;443:29-38.
7. Maeda D, Kanzaki Y, Sakane K, Tsuda K, Akamatsu K, Hourai R, et al. Prognostic value of the liver fibrosis marker fibrosis-5 index in patients with acute heart failure. ESC Heart Failure. 2022;9:1380-7.
8. Yoshihisa A, Sato Y, Yokokawa T, Sato T, Suzuki S, Oikawa M, et al. Liver fibrosis score predicts mortality in heart failure patients with preserved ejection fraction. ESC heart failure. 2018;5:262-70.
9. Chen S, Zhu B, Luo Z, Wang Y, Hu Q, Zhou L. The fibrosis-5 index predicts major adverse cardiovascular events in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention. Angiology. 2024:00033197241231051.
10. Valbusa F, Bonapace S, Agnoletti D, Scala L, Grillo C, Arduini P, et al. Nonalcoholic fatty liver disease and increased risk of 1-year all-cause and cardiac hospital readmissions in elderly patients admitted for acute heart failure. PLoS One. 2017;12:e0173398.
11. Barbosa JV, Milligan S, Frick A, Broestl J, Younossi Z, Afdhal N, et al. Fibrosis-4 index can independently predict major adverse cardiovascular events in nonalcoholic fatty liver disease. Official journal of the American College of Gastroenterology| ACG. 2022;117:453-61.
12. Takae M, Fujisue K, Yamamoto E, Egashira K, Komorita T, Oike F, et al. Prognostic significance of liver stiffness assessed by fibrosis-4 index in patients with heart failure. ESC heart failure. 2021;8:3809-21.

 doi:10.20944/preprints202411.1578.v1

13. Aspromonte N, Fumarulo I, Petrucci L, Biferali B, Liguori A, Gasbarrini A, et al. The liver in heart failure: from biomarkers to clinical risk. International Journal of Molecular Sciences. 2023;24:15665.
14. Wang Z, Li G, Huang R, Chang L, Gong C, Chen K, et al. Prognostic value of fibrosis-5 index combined with C-reactive protein in patients with acute decompensated heart failure. BMC Cardiovascular Disorders. 2023;23:492.
15. Peters AE, Pandey A, Ayers C, Wegermann K, McGarrah RW, Grodin JL, et al. Association of liver fibrosis risk scores with clinical outcomes in patients with heart failure with preserved ejection fraction: findings from TOPCAT. ESC heart failure. 2021;8:842-8.
16. Seo Y-G, Polyzos SA, Park K-H, Mantzoros CS. Fibrosis-4 index predicts long-term all-cause, cardiovascular and liver-related mortality in the adult Korean population. Clinical Gastroenterology and Hepatology. 2023;21:3322-35.
17. Cao M, Li T, Li Z, Gong F, Chen Z. A retrospective study on the relationship between fibrosis‐4 index and all‐cause mortality in patients with acute myocardial infarction. Experimental and Therapeutic Medicine. 2022;24:1-7.
18. Kogame T, Seo M, Yamada T, Yano M, Hayashi T, Nakagawa A, et al. Comparison of Prognostic Value of Liver Dysfunction Scores and Serum Cholinesterase Level in Acute Decompensated Heart Failure Patients with Preserved Left Ventricular Ejection Fraction: Insights from Pursuit-hfpef Registry. Circulation. 2021;144:A11011-A.