The association between non-clinically apparent liver fibrosis and pulmonary arterial hypertension in Hispanic patients

M Ammar Kalas
Texas Tech University Health Sciences Center El Paso
Yacoub Khatab
Texas Tech University Health Sciences Center El Paso
Gian Galura
Texas Tech University Health Sciences Center El Paso
Haider Alkhateeb
Texas Tech University Health Sciences Center El Paso
Debabrata Mukherjee
Texas Tech University Health Sciences Center El Paso
Hernando Garcia
Mount Sinai Medical Center
Marc Zuckerman
Texas Tech University Health Sciences Center El Paso
Nils Nickel (np.nickel@ttuhsc.edu)
Texas Tech University Health Sciences Center El Paso

Research Article

Keywords: pulmonary arterial hypertension, liver fibrosis, non-alcoholic fatty liver disease fibrosis score, non-invasive assessment

Posted Date: July 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1842484/v1

Abstract

Background:

Pulmonary arterial hypertension (PAH) is a deadly cardiopulmonary disease with multi-organ involvement including impaired liver function. Liver dysfunction in PAH is poorly understood but significantly associated with morbidity and mortality. Hispanics have a significantly higher prevalence of non-alcoholic fatty liver disease (NAFLD) and evidence of more advanced disease in comparison to other ethnic groups. The clinical impact of NAFLD in Hispanic PAH patients is unknown. We aimed to investigate the impact of a validated scoring system, non-alcoholic fatty liver disease fibrosis (NFS) score, to predict the degree of liver fibrosis in a Hispanic PAH population and its relationship to hemodynamics, functional class, and outcomes.

Methods:

A retrospective review of all treatment naïve Hispanic patients with group I WHO pulmonary hypertension (PH) at a single academic center between February 2016 and March 2021 was performed. Patients with history of substance or alcohol abuse, non-group I WHO PH, pre-existent liver disease, chronic kidney disease, atrial fibrillation, thyroid disease, and warfarin use were excluded from the study. The diagnosis of group I WHO PH was determined by cardiac catheterization after the exclusion of other etiologies. NFS scores were calculated for each patient and correlated with functional capacity, hemodynamics, NT-proBNP, and survival.

Results:

A total of 96 Hispanic patients were included in our study. The median age of patients in our cohort was 49 (IQR 15) and 69% of our cohort were females. Higher NFS scores indicating advanced hepatic fibrosis (F3-F4) were found to correlate with elevated right-sided cardiac filling pressures, elevated levels of NT-proBNP, lower functional capacity, and worse 5-year survival rates.

Conclusion:

In Hispanic patients with PAH, NFS scores correlate with the degree of right sided pressure overload. In addition, advanced fibrosis scores were independently associated with lower 5-year survival rates and added prognostic information to other established risk parameters in PAH. This study suggests that screening for liver disease in this vulnerable patient population can aid in earlier detection and possible intervention, thus leading to potential improvement in survival rates.

Background:

Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure (mPAP) greater than 20mmHg without exertion. This is confirmed by right heart catheterization(1). Hemodynamically, pulmonary hypertension can be broadly classified into 3 groups: pre-capillary (pulmonary arterial

hypertension (PAH)), post-capillary, or mixed. Pre-capillary and post-capillary pulmonary hypertension can be differentiated based on the pulmonary vascular resistance (≥ 3 woods units in pre-capillary PH) and pulmonary capillary wedge pressure (PCWP) (less than 15mmHg for pre-capillary). Clinically, PH can be classified into 5 subgroups; group 1 being pulmonary arterial hypertension (PAH), group 2 being PH due to left heart disease, group 3 being PH due to pulmonary disease, group 4 being PH due to chronic thromboembolic disease, and group 5 being miscellaneous causes such as complex congenital heart disease(2). PAH is a pre-capillary form of PH which has recently been regarded as a multisystem disease rather than a purely pulmonary entity(3).

Due to the elevations in right ventricular (RV) pressures in PH, upstream clinical and biochemical effects are expected. The liver is one of the first organs affected by elevated RV pressures resulting in abnormalities in liver biochemical tests and ascites(4). The lung-liver relationship is reciprocal: elevated right-sided filling pressures from PH are associated with congestive hepatopathy. Similarly, liver disease clearly has implications on the anatomy and function of the pulmonary circulation, as seen in porto-pulmonary hypertension, hepato-pulmonary syndrome(5), and Fontan physiology(6).

The relation between PH and non-clinically apparent liver fibrosis has not been evaluated directly in the past. In this study, we retrospectively reviewed a cohort of Hispanic PAH patients in a single academic center and correlate hemodynamic parameters, functional capacity, biochemical variables, and outcomes with the non-alcoholic fatty liver disease fibrosis scores (NFS).

This study aims to assess the prevalence of liver fibrosis based on non-invasive NFS scores in Hispanic patients with PAH and the relationship of fibrosis with hemodynamic, functional, and biochemical variables of disease severity as well as 5-year survival.

Methods:

A single center retrospective cohort study consisting of 96 treatment naïve Hispanic patients with World Health Organization (WHO) group 1 PH (PAH) from the PAH registry at Texas Tech University Health Sciences Center El Paso (TTUHSCEP) pulmonary hypertension clinic and University Medical Center (UMC) of El Paso, seen between February 2016 and March 2021. Exclusion criteria were; non-WHO group 1 PH, non-Hispanics, documented pre-existing liver disease (based on ICD-10 codes and physician documentation), a history of substance or alcohol abuse, chronic kidney disease, atrial fibrillation, thyroid disease, warfarin use. Each chart was independently reviewed by two investigators and was validated by the treating pulmonary hypertension physician. In all patients, the diagnosis of PAH was made by right heart catheterization and exclusion of other forms of PH by laboratory studies, echocardiography, pulmonary function testing, computed tomography angiography, and ventilation–perfusion scanning. Ethnicity was determined by self-reporting and primary language used during clinic encounters. All patients were seen and treated at the UMC El Paso and TTUHSCEP pulmonary hypertension clinic. Patients were monitored by regular outpatient visits for a median of 3.6 years (range 3 month to 60

months). Survival status was censored on May 31 2022. The primary end-point of this study was 5-year survival after the diagnosis of PAH.

Fibrosis scores (NFS) were calculated using the following formula: 1.675 + (0.037 × age (years)) + (0.094 × body mass index (kg/m2)) + (1.13 × diabetes (yes = 1, no = 0)) + (0.99 × AST/ALT ratio) – (0.013 × platelet (× 109/L)) – (0.66 × albumin (g/dL)). NFS scores below − 1.455 correlate with histological fibrosis stage F0–F2 with a negative predictive value of 88–93% for advanced fibrosis. NFS scores between − 1.455 and 0.675 are considered indeterminate, and NFS > 0.675 correlates with F3–F4 histological fibrosis with a positive predictive value of 82–90% for advanced fibrosis. The staging of the fibrosis was based on the histological Brunt criteria. The criteria includes 5 separate stages; stage 0 = absent fibrosis, stage 1 = portal or perisinusoidal fibrosis, stage 2 = portal/periportal and perisinusoidal fibrosis, stage 3 = bridging or septal fibrosis, and stage 4 = cirrhosis(7). Patients in this cohort were divided based on NFS scores; group 1 was considered negative for advanced fibrosis (NFS score < -1.455), group 2 was considered indeterminate (NFS score − 1.455–0.675), and group 3 was considered advanced fibrosis (NFS > 0.675). NFS scores (one score calculated per patient) were calculated within 3 months of the initial right cardiac catheterization, functional class assessment, and six-minute walking distance.

Patients' records were reviewed for any abdominal imaging obtained (ultrasonography, computed tomography, or liver transient elastography). However, the majority of patients did not have imaging studies and hence this variable was not included in the analysis.

All data are reported as absolute numbers, percentages, mean (SD), or median (IQR), as indicated. The relationship between NFS scores and baseline variables was assessed using Mann-Whitney U testing for continuous variables and Chi-Square testing for nominal or categorical variables. Correlations between continuous variables was assessed using the Pearson correlation coefficient. Spearman rank correlation was used to assess the correlation for nominal and categorical variables. Kaplan-Meier survival analysis was used to estimate overall survival in patients with low and high NFS scores. Log-rank testing was used to assess for statistical significance between both groups. Cox-regression analysis was used to identify non-invasive predictors of death during follow up. All variables were tested for normality of distribution using Kolmogorov-Smirnov testing. Variables without normal distribution were transformed into their natural logarithm before Cox analysis. A p-value of less than 0.05 was considered statistically significant. All calculations and graphics were done using SPSS 27 (IBM), Excel (Microsoft), and Graph pad (8.0.0 GraphPad software, San Diego, California).

Results:

Out of a database with 236 patients with pulmonary arterial hypertension, we identified 96 treatment naïve Hispanic patients (69% females) with PAH who met inclusion criteria (Figure 1). Median age was 49 years (IQR 15). Estimated median survival of the entire cohort was 3.9 years with survival percentages of 89.5% at one year, 77.4% at 3 years, and 68.7% at five years respectively. The clinical characteristics and

NFS scores are listed in table 1. The majority of patients in our cohort (37.5%) had F0-F2 stage of fibrosis according to the NFS score. Twenty-eight percent of patients had a NFS score (F3-F4) suggestive of advanced liver fibrosis. The remainder of the patients (34.4%) had an indeterminate NFS score and were excluded from further analysis due to the ambiguity of the clinical relevance of the score in these cases. Patients with advanced fibrosis score were older (48 versus 59 years, $p=0.05$), predominantly male (45% versus 14% in the mild fibrosis group, $p<0.05$), had a significantly worse WHO-FC (2.4 versus 2.9, $p<0.05$), 6-minute walk distance (6mwd) (288 meters versus 399 meters, $p<0.05$), higher NT-proBNP levels (1050 versus 2323, $p<0.05$), elevated right sided filling pressures (mRA 11.5mmHg versus 8mmHg, $p<0.05$), and elevated total bilirubin (0.6 versus 1.0, $p<0.05$). The correlation between the NFS score and patient variables is depicted in table 2.

Table 1. Baseline Characteristics and NFS score

	All patients (n=96)	Low NFS Score (F0-F2) (n=36)	Advanced NFS Score (F3-F4) (n=27)	p-value
Age (years)	49 (15)	48 (7)	59 (12)	0.014
Female [%]	69	86	55	<0.05
BMI [kg/m2]	30.2 (12)	27.1 (12)	32.1 (22)	0.35
WHO-FC [I-IV]	2.3 (±0.9)	2.4 (±0.6)	2.9 (±0.7)	<0.05
mRAP [mmHg]	8 (14)	8 (6-13)	11.5 (8-18)	<0.05
mPAP [mmHg]	42 (12)	38 (24-47)	43 (33-52)	0.19
PCWP [mmHg]	9 (5)	10 (7)	11 (5)	0.60
CI [l/min/m2]	2.4 (0.8)	2.9 (0.9)	2.7 (1.2)	0.41
6mwd [meters]	358 (178)	399 (178)	288 (184)	<0.05
NTproBNP [ng/l]	1853 (1856)	1050 (1178)	2323 (2773)	<0.05
NFS Score	-0.55 (2.5)	-2.6 (1.1)	1.4 (2.5)	<0.05
Platelets [ul]	208 (138)	295 (142)	143 (70)	<0.05
Albumin [g/dL]	3.5 (0.6)	3.6 (0.5)	3.4 (0.6)	0.821
AST [u/l]	31 (16)	26 (15)	43 (27)	0.23
ALT [u/l]	30 (21)	29 (18)	38 (27)	0.35
ALP [u/l]	92 (44)	95 (48)	89 (43)	0.46
tBili [mg/dl]	0.99 (0.5)	0.6 (0.4)	1.0 (0.8)	<0.05
Diabetes	26 (27.1)	5 (13.9)	14 (42)	<0.05

Data are shown as median (interquartile range) except for sex (%) and WHO-FC (mean SD).

P values between mild and advanced NAFLD patients were calculated by MANN-WHITNEY U Test for continuous variables, Chi-Square for differences in gender and t test for WHO-FC. Data are available for all patients, except data on CI are available for 80 patients in the entire cohort, 30 patients in the mild NAFLD group and 19 patients in the advanced NAFLD group. Data on 6mwd are available for 84 patients in the entire cohort and 33 patients in the mild NAFLD group.

BMI: body mass index, WHO-FC: World Health Organization Functional Class, mRAP: mean right atrial pressure, mPAP: mean pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, CI: cardiac

index, NFS: non-alcoholic fatty liver disease fibrosis score, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, tBili: total bilirubin.

Table 2. Correlation of NFS Score with baseline variables

	NFS Score (F0-F4)
Age (years)	0.342, 0.041
Gender	0.355, 0.009
BMI [kg/m2]	0.131, 0.350
WHO-FC [I-IV]	0.35, 0.005
mRAP [mmHg]	0.273, 0.031
mPAP [mmHg]	0.21, 0.27
PCWP [mmHg]	-0.073, 0.69
CI [l/min/m2]	-0.117, 0.423
6mwd [meters]	-0.485, 0.001
NTproBNP [ng/l]	0.321, 0.010

Correlations between continuous variables were assessed using the Pearson correlation coefficient. Spearman rank correlation was used to assess the correlation for nominal and categorical variables.

BMI: body mass index, WHO-FC: World Health Organization Functional Class, mRAP: mean right atrial pressure, mPAP: mean pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, CI: cardiac index, NFS: non-alcoholic fatty liver disease fibrosis score, 6mwd: 6-minute walking distance.

Estimated median survival was significantly reduced in patients with advanced fibrosis scores (4.6 years versus 3.0 years, $p<0.01$). Cox-regression analysis showed that NFS scores were significantly associated with survival in a univariate model (HR 2.3, $p=0.002$). Other significant non-invasive predictors of mortality at baseline were NT-proBNP (HR 1.2, $p=0.001$), albumin (HR 2.1, $p=0.001$), 6mwd (HR 1.1, $p=0.002$), and WHO-FC (HR 2.7, $p=0.001$). After adjusting for NT-pro-BNP, 6mwd, and WHO-FC, NFS scores remained significant predictors of poor outcomes (HR 2.0, $p=0.025$) (Table 3).

Table 3. Non-invasive risk assessment using Cox-regression analysis

	Univariate Model		Multivariate Model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
NFS Score	2.3 (1.8 – 3.7)	0.002	**2.0 (1.1-3.5)**	**0.025**
NT-proBNP	1.2 (1.1-1.4)	0.001	1 (0.9-1.1)	0.137
6mwd	1.1 (1.0-1.2)	0.002	0.98 (0.9-1.1)	0.395
WHO-FC	2.7 (1.8-3.5)	0.001	**1.7 (1.2-3.3)**	**0.028**

Cox-regression analysis was used to identify predictors of death during follow up.

WHO-FC: World Health Organization Functional Class, NFS: non-alcoholic fatty liver disease fibrosis score, 6mwd: 6-minute walking distance.

Kaplan Meier analysis showed that patients with advanced fibrosis scores had worse 5-year survival when compared with patients with low fibrosis scores (F0-F2) (Figure 2, log-rank <0.01).

Discussion:

The lung-liver relationship is reciprocal, and liver disease clearly has implications on the anatomy and function of the pulmonary circulation, as seen in porto-pulmonary hypertension, hepato-pulmonary syndrome(5) and Fontan physiology(6). Vice versa, right heart strain has significant clinical implications on liver function and liver dysfunction is common in PAH patients(4). The exact pathophysiology of liver dysfunction in PAH is poorly understood: hepatic congestion from right heart pressure overload and alteration in inflammatory, hormonal and genetic pathways have been implicated(4). Non-alcoholic fatty liver disease (NAFLD) is a clinicopathologic liver disease with a wide histological spectrum ranging from simple steatosis to cirrhosis and is associated with increased morbidity and mortality(8) .

The NFS score was initially created in 2007 as a non-invasive assessment for liver fibrosis in patients with NAFLD and was found to have a negative predictive value of advanced fibrosis (88–93%) when the lower cut-off was used (<-1.455), and a high positive predictive value of advanced fibrosis (82–90%) when the higher cut-off was used (> 0.675)(9). NFS scores were found to have a strong correlation with mortality, cardiovascular events, atheromatous plaque formation, and impaired renal function(10, 11). NFS score has been validated as a non-invasive tool of assessing hepatic fibrosis with the use of routinely ordered labs.

To date, the incidence and prevalence of liver fibrosis in Hispanic patients with PAH is unknown. In our cohort 27% of patients had signs of advanced fibrosis based on NFS scores. A retrospective analysis of ICD-10 codes in over 9 thousand patients with PH found that 7% carried a diagnosis of NAFLD (12). The prevalence of NAFLD in patients with chronic heart failure has been reported between 25 and 37%(13–15). This indicates that NAFLD is likely an underreported and underrecognized comorbidity in heart failure patients, including patients with PAH. Our data support the notion that especially Hispanic PAH

patients are at high risk for NAFLD. Despite analyzing a female predominant cohort, advanced fibrosis scores were more frequent in male patients. This is in line with other studies that found an increasing male prevalence with higher fibrosis scores(13). In patients without evidence of heart failure, the NAFLD prevalence seems to be higher in men, when compared with premenopausal women, however this relationship seems to be reversed when men are compared to postmenopausal women(16), implicating protective effects of female hormones on the liver. Our cohort had a median age of 49, it is therefore possible that premenopausal females had some protection against NAFLD development. Young females at childbearing age are at heightened risk for the development of PAH but seem to have a better overall prognosis when compared to male counterparts(17–20). This conundrum has been termed the “estrogen paradox” in PAH. The survival in PAH is mainly determined by the ability of the RV to cope with increased afterload, and improved survival in females was linked to enhanced RV function, implicating that estrogens might have protective effects on the RV(21). It is therefore possible that in PAH, female hormones protect the liver by advantageous hepatic fat metabolism(22) and by reduced congestion due to improved RV function.

Primary NAFLD has a strong association with metabolic syndrome (MS)(8). In patients with MS, insulin resistance and subsequent hyperinsulinemia are associated with altered glucose and lipid metabolism and subsequently, hepatic lipid accumulation leading to steatohepatitis(23, 24). The metabolic syndrome is characterized by elevated VLDL, LDL, TGs, hepatic insulin resistance, low-grad systemic inflammation, and decreased liver insulin extraction (25–27). In patients with advanced cirrhosis, disturbed hepatic blood flow has been linked to IR and hyperinsulinemia(28, 29). Recent data implicate that even though PAH patients have many clinical features of the MS, significant differences exist. For instance, elevated serum TGs levels, peripheral and hepatic insulin resistance are not classic features of PAH metabolism(4). In fact, congestive hepatopathy from right heart failure is associated with reduction in HDL production and increased hepatic insulin clearance(30). MS is a shared risk factor for NAFLD and heart failure (31) and the cause-and-effect relationship between liver fibrosis and cardiac dysfunction is a matter of ongoing research. There is evidence that NAFLD increases the risk for heart failure(31). Our study supports the notion that cardiac dysfunction plays a central role in the development of liver fibrosis. Right heart failure leads to increased pressure in the sublobular hepatic veins producing sinusoidal congestion, that may result in bridging fibrosis between adjacent central veins(32). These histopathological findings are not only seen in right heart failure but have also been described in patients with diastolic dysfunction(33).

In our cohort, advanced NFS scores were associated with survival in univariate and multivariate analysis, when adjusted for established non-invasive risk predictors (NT-proBNP, WHO-FC, 6mwd). Advanced NFS scores were significantly related to age, male gender, worse WHO-FC, lower 6mwd, elevated right arterial pressures and NT-proBNP levels, indicating that NFS scores assimilate several clinical, functional, hemodynamic and biochemical indicators of poor PAH outcomes. It is therefore interesting to note, that NFS scores added prognostic value to the established non-invasive risk parameters (Cox-regression). It is unclear if liver fibrosis score is a modifiable risk factor in PAH. To date, there are no approved medical therapies for liver fibrosis. Many pharmaceutical and dietary interventions are currently investigated to

treat liver fibrosis, their role in PAH-associated hepatic dysfunction is unclear(34). Anti-coagulation to restore congested liver blood flow has been shown to have beneficial effects in patients with advanced cirrhosis(35). The use of anticoagulants has also been implicated in improving survival in patients with idiopathic PAH(36, 37). This is certainly an area that will require further investigation via clinical trials, since the decision to use anti-coagulants in PAH needs to involve an individualized risk-benefit assessment. Other clinical considerations in patients with PAH and elevated NFS scores are correction of risk factors for liver disease and reduction of right-sided filling pressures by optimizing PAH-targeted therapies and diuresis. Furthermore, special attention should be paid to nutrition counseling and weight loss in obese patients.

Limitations:

Our study has several limitations, such as a relatively small cohort and its retrospective nature. Importantly, none of our patients had a liver biopsy to assess the degree of fibrosis. Our study lacks data on liver imaging (ultrasonography or computed tomography) that might be supportive of the NFS scores. Furthermore, our study did not investigate if PAH-targeted therapies are associated with changes in NFS scores.

Conclusion:

Especially older Hispanic male patients with PAH are at high risk for developing advanced liver fibrosis, which emerged as an independent risk factor for poor outcomes. Right heart strain seems to be an important contributor to liver fibrosis in PAH. Further research is needed to better understand the complex relationship between the lungs and liver in PAH, and to investigate if reducing NFS scores is a modifiable risk factor in PAH.

Abbreviations:

6mwd: 6-minute walk distance

mPAP: mean pulmonary arterial pressure

NAFLD: Non-alcoholic fatty liver disease

NFS: Non-alcoholic fatty liver disease fibrosis score

PH: Pulmonary hypertension

PAH: Pulmonary arterial hypertension

PCWP: Pulmonary capillary wedge pressure

RV: right ventricle

TTUHSCEP: Texas Tech University Health Sciences Center El Paso

UMC: University Medical Center

WHO: World health organization

WHO-FC: World health organization functional class

Declarations:

Ethics approval:

IRB approval was sought and the study was exempt from formal IRB review in accordance with 45 CFR 46.104(d)(4)(iii): The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of “health care operations” or “research” as those terms are defined at 45 CFR 164.501. A HIPAA waiver has been approved under 45 CFR 164.512(i)(2)(ii). No identifiable health information is included in the manuscript. De-identified health information was used for the analysis.

TTUHSC El Paso IRB 00009946

Study IRB number: E22054

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

Funding:

None.

Authors’ contribution:

Concept and design of the work: MAK, NN, MZ, HA, DM, GG, YK, HG.

Analysis: NN.

Drafting the paper: MAK, NN.

Revising the paper: MAK, NN, MZ, HA, DM, GG, YK, HG.

Guarantor: NN.

Acknowledgements:

Not applicable.

References:

1. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1).
2. Condon DF, Nickel NP, Anderson R, Mirza S, de Jesus Perez VA. The 6th World Symposium on Pulmonary Hypertension: what's old is new. F1000Res. 2019;8.
3. Nickel NP, Yuan K, Dorfmuller P, Provencher S, Lai YC, Bonnet S, et al. Beyond the Lungs: Systemic Manifestations of Pulmonary Arterial Hypertension. Am J Respir Crit Care Med. 2020;201(2):148–57.
4. Nickel NP, Galura GM, Zuckerman MJ, Hakim MN, Alkhateeb H, Mukherjee D, et al. Liver abnormalities in pulmonary arterial hypertension. Pulm Circ. 2021;11(4):20458940211054304.
5. Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. Lancet. 2004;363(9419):1461–8.
6. Kendall TJ, Stedman B, Hacking N, Haw M, Vettukattill JJ, Salmon AP, et al. Hepatic fibrosis and cirrhosis in the Fontan circulation: a detailed morphological study. J Clin Pathol. 2008;61(4):504–8.
7. Brunt EM. Pathology of nonalcoholic steatohepatitis. Hepatol Res. 2005;33(2):68–71.
8. Powell EE, Wong VW, Rinella M. Non-alcoholic fatty liver disease. Lancet. 2021;397(10290):2212–24.
9. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846–54.
10. Yu X, Chen C, Guo Y, Tong Y, Zhao Y, Wu L, et al. High NAFLD fibrosis score in non-alcoholic fatty liver disease as a predictor of carotid plaque development: a retrospective cohort study based on regular health check-up data in China. Ann Med. 2021;53(1):1621–31.
11. Hsieh MH, Wu KT, Chen YY, Yang JF, Lin WY, Chang NC, et al. Higher NAFLD fibrosis score is associated with impaired eGFR. J Formos Med Assoc. 2020;119(1 Pt 3):496–503.
12. Jordens MS, Luedde M, Roderburg C, Demir M, Luedde T, Kostev K, et al. Pulmonary hypertension is associated with an increased incidence of NAFLD: A retrospective cohort study of 18,910 patients. J Intern Med. 2021;290(4):886–93.
13. 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 Fail. 2021;8(2):842–8.

14. Takahashi T, Watanabe T, Shishido T, Watanabe K, Sugai T, Toshima T, et al. The impact of non-alcoholic fatty liver disease fibrosis score on cardiac prognosis in patients with chronic heart failure. Heart Vessels. 2018;33(7):733–9.
15. 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 Fail. 2018;5(2):262–70.
16. Lonardo A, Nascimbeni F, Ballestri S, Fairweather D, Win S, Than TA, et al. Sex Differences in Nonalcoholic Fatty Liver Disease: State of the Art and Identification of Research Gaps. Hepatology. 2019;70(4):1457–69.
17. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010;122(2):164–72.
18. Hoeper MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. Int J Cardiol. 2013;168(2):871–80.
19. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation. 2010;122(2):156–63.
20. Shapiro S, Traiger GL, Turner M, McGoon MD, Wason P, Barst RJ. Sex differences in the diagnosis, treatment, and outcome of patients with pulmonary arterial hypertension enrolled in the registry to evaluate early and long-term pulmonary arterial hypertension disease management. Chest. 2012;141(2):363–73.
21. Jacobs W, van de Veerdonk MC, Trip P, de Man F, Heymans MW, Marcus JT, et al. The right ventricle explains sex differences in survival in idiopathic pulmonary arterial hypertension. Chest. 2014;145(6):1230–6.
22. Lee C, Kim J, Jung Y. Potential Therapeutic Application of Estrogen in Gender Disparity of Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis. Cells. 2019;8(10).
23. Angulo P. Nonalcoholic fatty liver disease and liver transplantation. Liver Transpl. 2006;12(4):523–34.
24. Angulo P. Nonalcoholic fatty liver disease. Rev Gastroenterol Mex. 2005;70 Suppl 3:52 – 6.
25. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract. 2014;2014:943162.
26. Tchkonia T, Thomou T, Zhu Y, Karagiannides I, Pothoulakis C, Jensen MD, et al. Mechanisms and metabolic implications of regional differences among fat depots. Cell Metab. 2013;17(5):644–56.
27. Meshkani R, Adeli K. Hepatic insulin resistance, metabolic syndrome and cardiovascular disease. Clin Biochem. 2009;42(13–14):1331–46.

28. Maruyama H, Kobayashi K, Kiyono S, Yokosuka O. Interrelationship between insulin resistance and portal haemodynamic abnormality in cirrhosis. Int J Med Sci. 2017;14(3):240–5.
29. Ishikawa T, Shiratsuki S, Matsuda T, Iwamoto T, Takami T, Uchida K, et al. Occlusion of portosystemic shunts improves hyperinsulinemia due to insulin resistance in cirrhotic patients with portal hypertension. J Gastroenterol. 2014;49(9):1333–41.
30. Melenovsky V, Benes J, Franekova J, Kovar J, Borlaug BA, Segetova M, et al. Glucose Homeostasis, Pancreatic Endocrine Function, and Outcomes in Advanced Heart Failure. J Am Heart Assoc. 2017;6(8).
31. Wijarnpreecha K, Lou S, Panjawatanan P, Cheungpasitporn W, Pungpapong S, Lukens FJ, et al. Association between diastolic cardiac dysfunction and nonalcoholic fatty liver disease: A systematic review and meta-analysis. Dig Liver Dis. 2018;50(11):1166–75.
32. Bayraktar UD, Seren S, Bayraktar Y. Hepatic venous outflow obstruction: three similar syndromes. World J Gastroenterol. 2007;13(13):1912–27.
33. Louie CY, Pham MX, Daugherty TJ, Kambham N, Higgins JP. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. Mod Pathol. 2015;28(7):932–43.
34. Weiskirchen R, Weiskirchen S, Tacke F. Recent advances in understanding liver fibrosis: bridging basic science and individualized treatment concepts. F1000Res. 2018;7.
35. Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012;143(5):1253-60 e4.
36. Khan MS, Usman MS, Siddiqi TJ, Khan SU, Murad MH, Mookadam F, et al. Is Anticoagulation Beneficial in Pulmonary Arterial Hypertension? Circ Cardiovasc Qual Outcomes. 2018;11(9):e004757.
37. Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R, et al. Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation. 2014;129(1):57–65.

Figures

Figure 1: Flow diagram of patient selection.

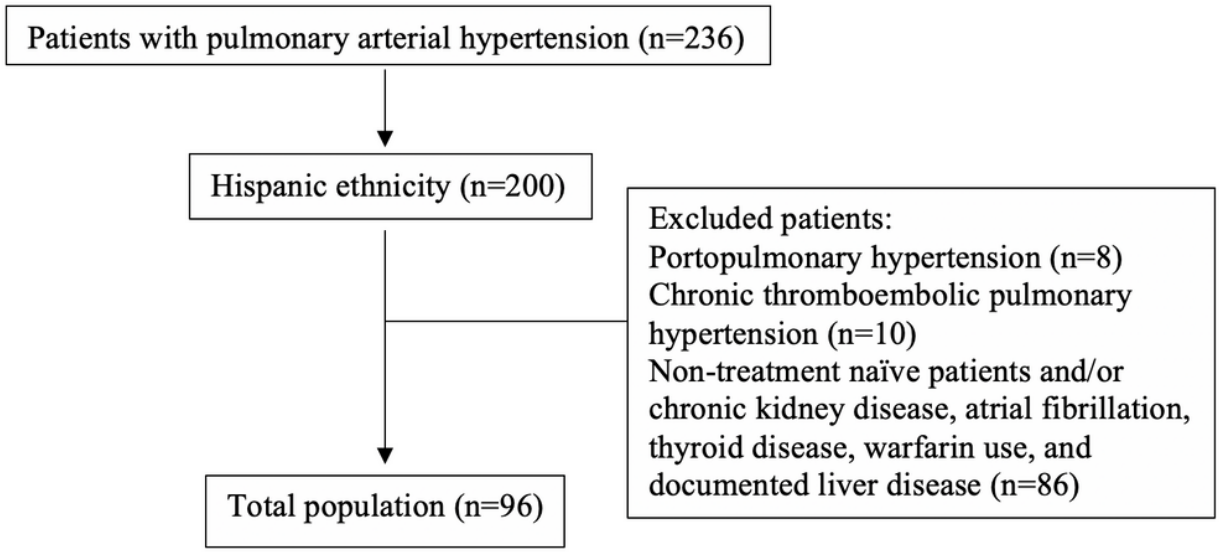

Figure 1

Flow diagram of patient selection.

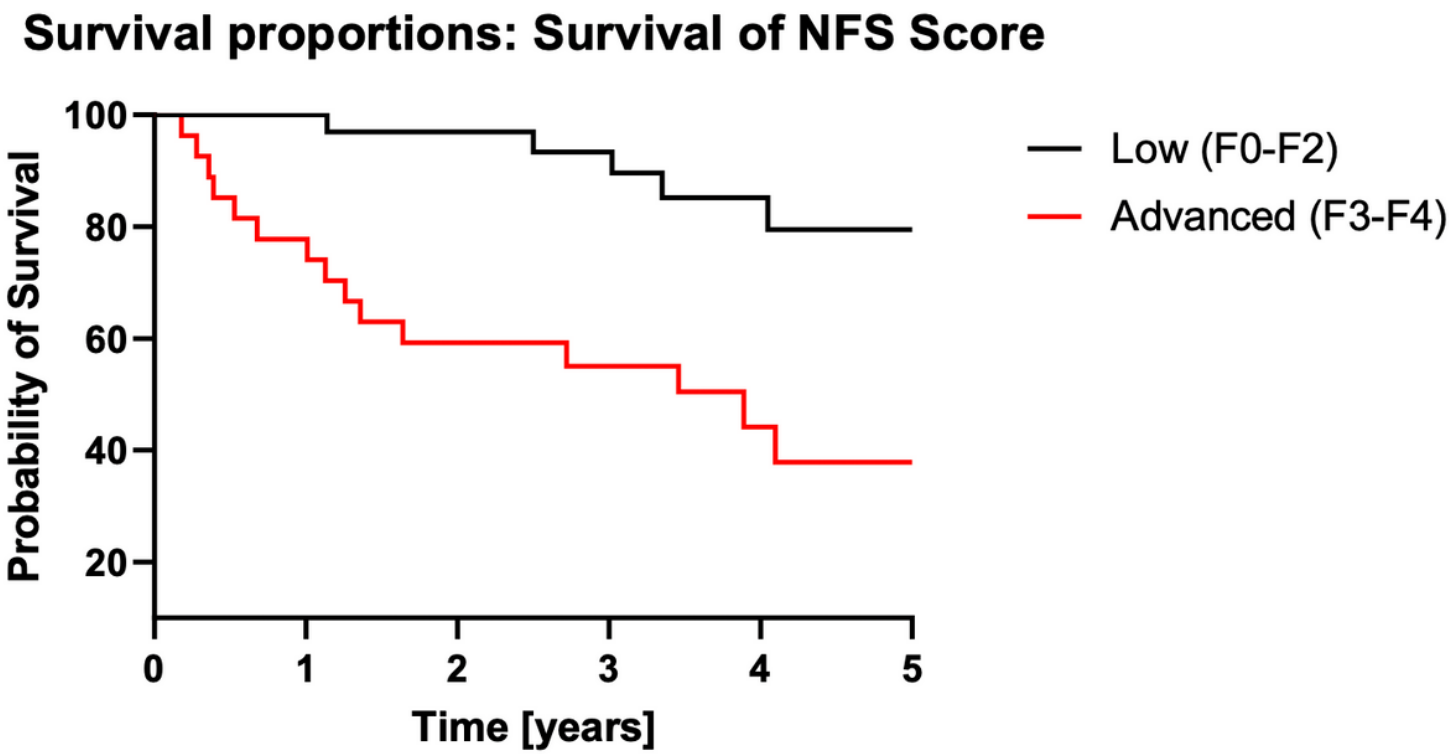

Figure 2

Kaplan-Meier Analysis according to negative and positive (advanced) fibrosis scores.