Testing the ability of the nonalcoholic fatty liver disease fibrosis score to predict 1-year all-cause hospital admission

Trace Heavener, DO^a , Ahmed Memon, BA^b, Shamyal Khan, DO^a, Sam Davis, DO^a , Lauren Sager, MS^c, Sharon DeMorrow, PhD^d, and Mark Jeffries, DO^e

^aDepartment of Medicine, Division of Internal Medicine, Scott & White Medical Center–Temple, Temple, Texas; ^bCollege of Medicine, Texas A&M University, Temple, Texas; ^cOffice of Biostatistics, Baylor Scott & White Research Institute–Temple, Temple, Texas; ^dDepartment of Medical Physiology, College of Medicine, Texas A&M University, and Research Biologist, Central Texas Veterans Healthcare System, Temple, Texas; ^eDepartment of Medicine, Division of Gastroenterology, Scott & White Medical Center–Temple, Temple, Texas

ABSTRACT

The nonalcoholic fatty liver disease fibrosis score (NFS) has been shown to be a cost-effective screening strategy in the primary care setting to determine when gastroenterology referral is needed, but NFS as a predictor of hospitalization within 1 year is uncertain. This retrospective observational cohort study involved 1803 patients with a diagnosis of nonalcoholic fatty liver disease or nonalcoholic steatohepatitis. The NFS was categorized into the following: low (less than -1.455), moderate (between -1.455 and 0.676), and high (>0.676). The average NFS score by hospital admission was -0.760 , the average number of admissions was 1.81, and the median number of days to hospital admission was 135.8 days (45.5–363, 25th to 75th percentile). A univariate logistic regression model showed that NFS significantly predicted hospital admission ($P=0.007$); however, a multivariate logistic regression model, after adjusting for hypertension and tobacco use, indicated that NFS was not significantly associated with hospital admission. Using the logistic regression model, hypertension predicted admission at low ($P<0.0001$) and moderate ($P=0.0005$) NFS. Using this same model, tobacco use also predicted admission at low ($P<0.0001$) and moderate ($P=0.0002$) NFS. The NFS should not be used to determine which patients are at increased risk of hospitalization.

KEYWORDS Hospitalization; hypertension; nonalcoholic fatty liver disease fibrosis score; preventive care; tobacco use

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of diseases ranging from reversible hepatic steatosis to nonalcoholic steatohepatitis and can lead to liver fibrosis. The most widely accepted noninvasive method to diagnose liver fibrosis in patients with NAFLD is the NAFLD fibrosis score (NFS).¹ An NFS indicating advanced fibrosis has been shown to be an independent predictor for all-cause mortality, need for liver transplant, presence of diabetes, cerebrovascular disease, chronic kidney disease, and cardiac disease.^{2–11} The NFS has been shown to be the most cost-effective strategy to predict severity of liver disease and cirrhosis and is an independent risk factor for hospitalization.^{12–14} Additionally, in elderly patients admitted with heart failure, NAFLD has been associated with a fivefold increased risk of 1-year all-cause rehospitalization.¹⁵ However, to our knowledge, no data exist on whether the NFS can be used as a predictor of all-cause

hospitalization within 1 year. Our aim was to determine whether, in patients with a diagnosis of NAFLD, the NFS correlates with 1-year increased risk of all-cause hospital admission.

METHODS

This was a retrospective observational cohort study design. Inclusion criteria screened patients aged 18 to 75 years with a diagnosis of NAFLD or nonalcoholic steatohepatitis in the outpatient setting, with laboratory results for NFS, between the dates of January 1, 2014, and December 31, 2015. Statistical analysis was performed in 2018. Exclusion criteria included a diagnosis of ascites, metabolic encephalopathy, and hepatocellular carcinoma. Patients who died were included in the final analysis. This study was deemed exempt from approval by the Baylor Scott and White institutional review board.

Corresponding author: Trace Heavener, DO, Department of Medicine, Division of Internal Medicine, Scott & White Medical Center–Temple, 2401 S. 31st St., Temple, TX 76508 (e-mail: trace.heavener@bswhealth.org)

Received August 3, 2018; Revised October 27, 2018; Accepted October 29, 2018.

Investigators screened charts with the aforementioned inclusion and exclusion criteria, taking note of outpatient laboratory results for aspartate aminotransferase, alanine aminotransferase, platelets, and albumin. After screening these records, additional data were collected, including age, gender, body mass index (BMI), previous diabetes or hypertension, statin use, tobacco use, primary diagnosis on hospital admission, days from calculation of NFS until hospital admission, and total number of hospital admissions from date of score in 1-year follow-up. Hypertension and smoking were two comorbidities common in the patient population and were diagnoses that primary care physicians have access to in their office when seeing the patient. Thus, these were chosen for further investigation via multivariate analysis.

Sample characteristics were described using descriptive statistics. Frequencies and percentages were used to describe categorical variables. Means and standard deviations (or medians and ranges where appropriate) were used to describe continuous variables. A chi-square test was used to test for associations in bivariate comparisons of categorical variables. Two-sample Wilcoxon tests were used to test for group differences in continuous variables. Logistic regression models were used to assess the significance of various predictors on hospital admission as well as obtain odds ratios (ORs) for the magnitude of risk for certain populations. A significance level of 0.05 was used to determine statistical significance. Spearman correlation was used to examine the relationship between each of the components of NFS. Baseline disease severity was determined by the NFS score, which was split into the categories of low (less than -1.455), moderate (-1.455 to 0.676), and high (>0.676).¹

RESULTS

A total of 1803 patients met the inclusion criteria for analysis, 686 with low NFS (mean score, -2.47), 826 with moderate NFS (mean score, -0.46), and 291 with high NFS (mean score, 1.66). Of these, 456 patients (25.3%) were admitted during the 1-year follow up, with only 3 admissions having a primary diagnosis of a liver issue. Most (62.72%) of our cohort was female, with an average BMI of 34 kg/m^2 , average age of 51.5 years, 39.04% with statin use, 50% with diabetes, and 24.34% with tobacco use. Our average NFS score by hospital admission was -0.760 . Among those who were admitted within 1 year of NFS laboratory results, the average number of admissions was 1.81. The median days from outpatient laboratory result to hospital admission was 135.8 days (45.5–363, 25th–75th percentile). The mean BARD scores for low, moderate, and high NFS were 1.251, 1.843, and 2.399, respectively. The mean aspartate aminotransferase-to-platelet ratio index scores for low, moderate, and high NFS were 0.346, 0.56, and 0.902, respectively. There were 199 patients with cirrhosis; of these, 29 (14.57%) had low NFS, 75 (37.69%) had moderate NFS, and 95 (47.74%) had high NFS.

Table 1. Comparison of patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis who were admitted or not admitted to the hospital within 1 year of nonalcoholic fatty liver disease fibrosis score results^a

Variable	Admitted (n = 456)	Nonadmitted (n = 1347)	P value
Age (years)	51.5 (41–60)	50 (40–59)	0.07
Body mass index (kg/m ²)	34 (28.95–40.25)	34.3 (29.9–39.2)	0.29
Men	170 (37.28%)	548 (40.68%)	0.2
Diabetes mellitus	228 (50.0%)	521 (38.68%)	<0.01
Statin use	178 (39.04%)	495 (36.75%)	0.38
Tobacco	111 (24.34%)	177 (13.14%)	<0.01
Hypertension	335 (73.46%)	767 (56.94%)	<0.01
AST (IU/L)	27 (19–44)	29 (20–47)	0.06
ALT (IU/L)	33.5 (22–57)	39 (24–69)	<0.01
Albumin (g/dL)	3.8 (3.5–4.1)	3.9 (3.6–4.2)	<0.01
Platelets (10 ⁹ /L)	240 (188–288)	237 (193–278)	0.53
Overall NFS	-0.76 (-1.77 to 0.4)	-1.02 (-2.03 to 0.06)	<0.01
High	91 (19.96%)	200 (14.85%)	
Moderate	215 (47.15%)	611 (45.36%)	
Low	150 (32.89%)	536 (39.79%)	

AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; NFS, nonalcoholic fatty liver disease fibrosis score.

^aContinuous variables are reported as medians (25th–75th percentile); categorical variables are reported as number (%).

A univariate logistic regression model showed that NFS significantly predicted hospital admission ($P=0.007$). Pairwise comparisons between NFS groups showed that patients with high NFS had significantly higher odds of hospital admission than patients with low NFS (OR = 1.63; confidence interval [CI], 1.20–2.21; $P=0.002$). However, when comparing patients with high versus moderate NFS (OR = 1.29; CI, 0.97–1.73; $P=0.09$) and moderate versus low NFS (OR = 1.26; CI, 0.99–1.60; $P=0.06$), there was not a statistically significant difference in hospital admission (Table 1).

A multivariate logistic regression model showed that hypertension and tobacco use were the only factors independently associated with NFS. Using this model, NFS was not significantly associated with hospital admission due to having the hypertension and tobacco confounding factors. Controlling for a patient's hypertension status revealed that NFS was not associated with hospital admission for patients with hypertension ($P=0.51$) or for patients without hypertension ($P=0.60$). Similarly, estimated odds of a patient being admitted to the hospital within 1 year of labs were 2.13 times higher for patients who abuse tobacco (CI, 1.63–2.78). Regardless of NFS status, patients with

Table 2. Odds of being admitted to the hospital based on hypertension and tobacco status combined with nonalcoholic fatty liver disease fibrosis score results

NFS	Variable	Number admitted	Total participants	Odds ratio	CI (95%)	P value
Low	Hypertension	90	310	2.16	(1.489, 3.117)	0.0001
	Tobacco	48	134	2.46	(1.629, 3.723)	0.0001
Moderate	Hypertension	163	546	1.87	(1.312, 2.655)	0.0005
	Tobacco	47	116	2.20	(1.460, 3.308)	0.0002
High	Hypertension	82	246	2.00	(0.920, 4.350)	0.08
	Tobacco	16	38	1.73	(0.859, 3.470)	0.13

CI indicates confidence interval; NFS, nonalcoholic fatty liver disease fibrosis score.

hypertension were 2.09 times more likely to be admitted to the hospital than patients without hypertension (CI, 1.66–2.65).

Logistic regression models were used to assess the predictive ability of hypertension and tobacco use on hospital admission for each of the three levels of NFS (*Table 2*). Among patients with a low NFS, a significant association with hospital admission was detected for hypertension ($P < 0.0001$) and tobacco use ($P < 0.0001$). Among patients with a low NFS, those with hypertension were 2.16 (1.49–3.12) times more likely to be admitted to the hospital than patients without hypertension. Patients who abused tobacco and had a low NFS score were 2.46 (1.63–3.72) times more likely to be admitted to the hospital than patients who did not abuse tobacco. Among patients with a moderate NFS, a significant association was also detected for hypertension ($P = 0.0005$) and tobacco use ($P = 0.0002$), with hospital admission OR estimates of 1.87 (1.31–2.66) for patients with hypertension and 2.20 (1.46–3.31) for patients who abuse tobacco. Among patients with a high NFS, a significant association was not detected for hypertension ($P = 0.08$) or tobacco use ($P = 0.13$).

Secondary factors associated with hospital admission that were found to be statistically significant included diabetes ($P < 0.0001$), decreased alanine aminotransferase ($P = 0.0002$), decreased albumin ($P < 0.0001$), hypertension ($P < 0.0001$), and tobacco ($P < 0.0001$). Several factors found to have no statistically significant association with hospital admission within 1 year of outpatient laboratory results included age ($P = 0.07$), BMI ($P = 0.29$), sex ($P = 0.20$), statin use ($P = 0.38$), aspartate aminotransferase ($P = 0.06$), and platelets ($P = 0.53$) (*Table 1*).

DISCUSSION

This retrospective observational cohort study found that NFS level alone was not a predictor of all-cause hospital admission. Hypertension and tobacco use were significantly related to NFS, which made NFS appear significantly related to hospital admission. After controlling for hypertension and tobacco use (i.e., stratifying to patients with and without

hypertension and tobacco use separately), there was no association between NFS and hospital admission. The NFS was only associated with hospital admission when ignoring hypertension and tobacco use. As soon as adjustments were made for hypertension and tobacco use, NFS became non-significant. The NFS was significantly associated with hypertension and tobacco use individually, and these independent risk factors were significantly associated with hospital admission. Hypertension, separate from tobacco use, and tobacco use, separate from hypertension, both significantly impacted hospital admission.

For other secondary factors associated with hospital admission such as alanine aminotransferase, platelets, and albumin, these results may have been statistically significant but were not clinically significant. The alanine aminotransferase level of those who were admitted (33.5 IU/L) was too close to that of those who were not admitted (39 IU/L) for primary care clinicians to distinguish clinically. Similarly, an albumin level of 3.8 versus 3.9 g/dL and a platelet level of 237 versus 240 $10^9/L$ were too indistinguishable to have clinical significance.

Many chronic disease such as NAFLD, chronic kidney disease, cerebrovascular disease, and diabetes advance slowly over decades.^{5,9,10,16} Thus, it is conceivable that a 1-year interval is too short of a time frame to examine. Future research could aim to identify whether a longer time interval, such as 5 or 10 years, would alter the results of this study. Another limitation to this study is selection bias, in that only charts within the Baylor Scott & White Health system (limited by geography, hospital not-for-profit status) were selected. It is likely that some patients sought care outside of this health system during the year. An attempt to mitigate this bias was made by including all charts within this system and using random sampling to determine the final charts included. This study was also prone to information bias due to possible lack of adequate, or inappropriate, classification of NAFLD or lab values. On rare occasions, laboratory tests could not all be taken from the same visit date; however, combinations were made within a reasonable amount of time. Unfortunately, there were a few cases in which missing

data did not allow for computation, and those accounts were removed from the analysis.

Federal programs are increasingly emphasizing quality outpatient care, such as the Centers for Disease Control and Prevention's Public Health Fund, established as part of the 2010 Affordable Care Act, which is tasked with improving health outcomes and decreasing costs.^{17,18} As health systems, insurers, employers, and the federal government are devoting an increasing amount of outpatient resources to avoid hospitalization,^{19,20} they may do well to understand that NFS alone does not increase this risk. Increased emphasis on adequate management of risk factors for NFS (namely, hypertension and tobacco use) should be of primary importance to avoid hospitalizations.

ORCID

Trace Heavener <http://orcid.org/0000-0002-1407-8736>

Sam Davis <http://orcid.org/0000-0002-1700-1048>

- Angulo P, Hui JM, Marchesini G. The NAFLD fibrosis score: a non-invasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology*. 2007;45(4):846–854. doi:10.1002/hep.21496.
- Le MH, Devaki P, Ha NB, et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. *PLoS One*. 2017;12(3):e0173499. doi:10.1371/journal.pone.0173499.
- McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut*. 2010;59(9):1265–1269. doi:10.1136/gut.2010.216077.
- Kim D, Kim WR, Kim HJ, Therneau TM. Association between non-invasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. *Hepatology*. 2013;57(4):1357–1365. doi:10.1002/hep.26156.
- Takahashi Y, Kurosaki M, Tamaki N, et al. Non-alcoholic fatty liver disease fibrosis score and FIB-4 scoring system could identify patients at risk of systemic complications. *Hepatol Res*. 2015;45(6):667–675. doi:10.1111/hepr.12405.
- Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2015;149(2):389–397.e10. doi:10.1053/j.gastro.2015.04.043.
- Treeprasertsuk S, Leverage S, Adams LA, Lindor KD, Sauver J, Angulo P. The Framingham risk score and heart disease in nonalcoholic fatty liver disease. *Liver Int*. 2012;32(6):945–950. doi:10.1111/j.1478-3231.2011.02753.x.
- Treeprasertsuk S, Björnsson E, Enders F, Suwanwalaikorn S, Lindor KD. NAFLD fibrosis score: a prognostic predictor for mortality and liver complications among NAFLD patients. *World J Gastroenterol*. 2013;19(8):1219–1229. doi:10.3748/wjg.v19.i8.1219.
- Sesti G, Fiorentino TV, Arturi F, Perticone M, Sciacqua A, Perticone F. Association between noninvasive fibrosis markers and chronic kidney disease among adults with nonalcoholic fatty liver disease. *PLoS One*. 2014;9(2):e88569. doi:10.1371/journal.pone.0088569.
- Doycheva I, Cui J, Nguyen P, et al. Non-invasive screening of diabetics in primary care for NAFLD and advanced fibrosis by MRI and MRE. *Aliment Pharmacol Ther*. 2016;43(1):83–95. doi:10.1111/apt.13405.
- Xun YH, Guo JC, Lou GQ, et al. Non-alcoholic fatty liver disease (NAFLD) fibrosis score predicts 6.6-year overall mortality of Chinese patients with NAFLD. *Clin Exp Pharmacol Physiol*. 2014;41(9):643–649. doi:10.1111/1440-1681.12260.
- Tapper EB, Hunink MG, Afdhal NH, Lai M, Sengupta N. Cost-effectiveness analysis: risk stratification of nonalcoholic fatty liver disease (NAFLD) by the primary care physician using the NAFLD fibrosis score. *PLoS One*. 2016;11(2):e0147237. doi:10.1371/journal.pone.0147237.
- Tapper EB, Sengupta N, Hunink MG, Afdhal NH, Lai M. Cost-effective evaluation of nonalcoholic fatty liver disease with NAFLD fibrosis score and vibration controlled transient elastography. *Am J Gastroenterol*. 2015;110(9):1298–1304. doi:10.1038/ajg.2015.241.
- Ho CK, Maselli JH, Terrault NA, Gonzales R. High rate of hospital admissions among patients with cirrhosis seeking care in US emergency departments. *Dig Dis Sci*. 2015;60(7):2183–2189. doi:10.1007/s10620-015-3594-z.
- Valbusa F, Bonapace S, Agnoletti D, 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(3):e0173398. doi:10.1371/journal.pone.0173398.
- Diehl AM, Day C. Cause, pathogenesis, and treatment of nonalcoholic steatohepatitis. *N Engl J Med*. 2017;377(21):2063–2072. doi:10.1056/NEJMra1503519.
- Office of Financial Resources. *Prevention and Public Health Fund*. Atlanta, GA: CDC. <https://www.cdc.gov/funding/pphf/index.html>. Updated January 5, 2017. Accessed March 25, 2018.
- Stremikis K, Connors C, Hoo E. *Intensive Outpatient Care Program: A Care Model for the Medically Complex Piloted by Employers*. New York, NY: The Commonwealth Fund; 2017. <http://www.commonwealthfund.org/publications/case-studies/2017/sep/intensive-outpatient-care-program>
- Kripalani S, Theobald CN, Anctil B, Vasilevskis EE. Reducing hospital readmission: current strategies and future directions. *Annu Rev Med*. 2014;65(1):471–485. doi:10.1146/annurev-med-022613-090415.
- Feachem RG, Sekhri NK, White KL. Getting more for their dollar: a comparison of the NHS with California's Kaiser Permanente. *BMJ*. 2002;324(7330):135–141. doi:10.1136/bmj.324.7330.135.