Published in final edited form as:

Liver Int. 2019 May ; 39(5): 933–940. doi:10.1111/liv.14018.

Atrial fibrillation is highly prevalent yet undertreated in patients with biopsy-proven Nonalcoholic Steatohepatitis

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Abstract

Background & Aims: Nonalcoholic steatohepatitis (NASH) is associated with increased cardiovascular disease. Atrial fibrillation is a prominent risk marker for underlying cardiovascular disease with a prevalence of 2% in patients < 65 years old. Atrial fibrillation prevalence in NASH is unknown. We sought to assess the prevalence and impact of atrial fibrillation on healthcare utilization in NASH.

Methods: Patients were identified from a tertiary care center Electronic Database from 2002–2015. International Classification of Diseases 9 (ICD9) codes identified comorbidities and atrial fibrillation. Descriptive statistics were used to compare characteristics between patients with NASH with and without atrial fibrillation.

Results: Of 9108 patients with ICD9 diagnosis of NASH, 215 (2.3%, mean age 57 years, 32% male) had biopsy-proven NASH. Atrial fibrillation prevalence was 4.6%. Patients with NASH and atrial fibrillation had a higher prevalence of heart failure (54.5% vs. 8.8%, $p<0.001$) and cerebrovascular (27.3% vs. 2.0%, $p<0.001$) or vascular disease (54.5% vs. 13.2%, $p=0.002$), compared to NASH without atrial fibrillation. All patients with NASH and atrial fibrillation had a CHA₂DS₂VASc score ≥ 2 indicating high stroke risk and need for anticoagulation. Eight of 10 patients were eligible for anticoagulation and 5 of 8 (62.5%) received appropriate therapy.

Conclusion: Atrial fibrillation prevalence is two-fold higher in patients with NASH compared to the general population. Patients with NASH have a high risk of stroke; however, many do not receive appropriate guideline-directed therapy. Future studies are needed to identify whether

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Conflict of interest: The authors of this study have no conflicts of interest to address. The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Institutes of Health

Statement of financial support: Dr. VanWagner is supported by the National Institutes of Health's National Heart, Lung, and Blood Institute, Grant Number K23HL136891

guideline-based management of atrial fibrillation in NASH reduces cardiovascular morbidity and mortality.

Lay summary:

Atrial fibrillation (AF) prevalence among patients with nonalcoholic steatohepatitis (NASH) is two-fold higher than the general population. Patients with NASH and AF have higher comorbidity burden and hospitalization utilization than patients with NASH without AF. The majority of patients with NASH and AF have a high stroke risk, yet in our cohort only 62.5% of patients received guideline-recommended therapy aimed at reducing cardiovascular morbidity and mortality.

Keywords

NASH; NAFLD; arrhythmia; cardiovascular disease

Introduction:

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among patients with nonalcoholic fatty liver disease (NAFLD) and its severe form, nonalcoholic steatohepatitis (NASH) which may lead to hepatic fibrosis and cirrhosis.¹ Hepatic fibrosis increases risk for liver-related and CVD mortality in patients with NAFLD/NASH. Atrial fibrillation (AF) is the most common type of cardiac arrhythmia. An estimated 3.03 million people in the United States have AF, and the prevalence increases as patients age ranging from 0.5 to 12%.^{2,3} The inflammatory milieu of NAFLD⁴⁻⁶ may contribute to cardiac remodeling and lead to the development of arrhythmias.^{7,8} Recently, Targher et al. demonstrated in two separate studies that NAFLD, diagnosed by ultrasonography, is associated with an increased prevalence and incidence of AF among patients with type 2 diabetes.^{9,10} In a prospective population-based study from Finland, researchers also found that ultrasound-diagnosed NAFLD was independently associated with the risk of incident AF independent of confounders including age, sex, body mass index (BMI), and diabetes status.¹¹ However, these findings have not been replicated in all population-based large cohorts. For example, the Framingham Heart Study and Study of Health in Pomerania (SHIP) showed no association between AF and either computerized tomography (CT) or ultrasound-diagnosed hepatic steatosis.^{12,13} The prevalence and impact of AF in biopsy-proven NASH is unknown.

Most studies which examine clinical outcomes in patients with AF and coexisting liver disease are derived from the transplant population. Patients with AF who undergo liver transplantation have increased cardiovascular morbidity and mortality, greater need for post-operative intensive care unit level care, and lengthier hospitalizations.¹⁴⁻¹⁷ There is a paucity of data which specifically examine the impact of AF on healthcare utilization in the non-transplant NASH population. Because patients with NASH have risk factors for the development of cardiac abnormalities, it is prudent to better characterize this group further to fully understand how management of these patients might impact morbidity and mortality.

The purpose of the current study was to determine the prevalence of AF among patients with NASH, to assess the impact of AF on healthcare utilization in patients with NASH, and to determine what, if any, guideline-based therapy patients with concomitant NASH and AF are receiving. We hypothesized that given the propensity for patients with NASH to develop arrhythmias, the prevalence of AF in patients with NASH will exceed that of the general population. Additionally, patients with NASH and AF will have a higher comorbidity burden and healthcare utilization than patients with NASH alone.

Methods:

This is a retrospective cohort study of all adult (age ≥ 18 years) patients with biopsy-proven NASH who were evaluated at a large tertiary care center between February 2002 and December 2015. Clinical and demographic information was extracted from patient charts through the Northwestern Medicine Enterprise Database Warehouse, a repository of clinical and research data for the Northwestern Medicine health system. The diagnosis of NASH/NAFLD was determined using an International Classification of Diseases, the 9th Revision, Clinical Modification (ICD-9-CM) algorithm adopted from Reddy et al.¹⁸ All patients with ICD-9-CM billing code diagnosis of NASH/NAFLD were then additionally searched for the presence of liver biopsy pathology reports to identify the biopsy-proven NASH cohort. Pathology reports from liver biopsies performed at our institution were independently reviewed (M.W.; L.V.), and those with a diagnosis of biopsy-proven NASH, defined as the presence of steatohepatitis on pathology read, or biopsy-proven cirrhosis thought secondary to NASH (e.g., cirrhosis on biopsy plus an ICD9 code for NAFLD/NASH), were included in the biopsy-proven NASH study cohort. Prevalent comorbidities, including AF (ICD9-CM 427.31x) were identified from the electronic medical record. Medication and documented reasons for not prescribing indicated therapy were manually reviewed. Guideline-recommended therapy for AF was defined as a patient having a Class I indication for warfarin or a direct thrombin or factor Xa inhibitor according to Clinical Practice Guidelines for patients with atrial fibrillation.¹⁹ Laboratory data were used to calculate CHA2DS2VASc score, a risk stratifying tool which incorporates stroke risk factors and modifiers to determine if anticoagulation is indicated for the reduction of stroke risk.²⁰ To determine hospitalization data, intensive care unit (ICU) admission, and rate of re-hospitalization, discharge diagnoses were searched. To determine AF prevalence among a comparator cohort of patients without NASH seeking care at a tertiary care center, we identified all adult patients age < 65 years who were evaluated at our institution between February 2002 and December 2015 without a diagnosis of NAFLD/NASH, stratified by AF status. AF prevalence in the general population for adults age < 65 years was determined from previously published literature.

The primary outcomes were prevalence of AF and the prevalence of patients on guideline-recommended therapy for AF.²¹ Secondary outcomes included total hospitalizations, total number of ICU stays, and length of hospitalization. The study was approved by the Northwestern Institutional Review Board. A waiver of informed consent was granted due to the retrospective study design and minimal risk to participants.

Statistical Methods:

To summarize the clinical characteristics of patients with NASH, descriptive statistics (count and percentage for categorical variables and mean (standard deviation) for continuous variables) were presented for each of the characteristics. To compare the difference between patients with NASH with and without AF, we performed chi-square or Fisher's exact test for categorical variables and two-sample t-tests for continuous variables. All analyses were performed using R 3.5.0. A p value of <0.05 was considered statistically significant.

Results:

Of 9108 patients with NAFLD/NASH by ICD-9 code alone, 514 had concomitant AF for an AF prevalence of 5.6%; the prevalence among those < 65 years of age was 4.2%. We identified 215 patients with biopsy-proven NASH at our institution. Of the biopsy-proven NASH cohort, the overall prevalence of AF was 4.6% (n=10) and the AF prevalence among those < 65 years of age was 4.0% (n=7 of 174). For comparison, we also identified 111,812 patients < 65 years of age without NAFLD/NASH by ICD-9 code, of whom 3,057 had a diagnosis of AF for an AF prevalence of 2.7%. (Figure 1).

The demographic characteristics of patients with biopsy-proven NASH stratified by AF status are shown in Table 1. Of the 10 patients with biopsy-proven NASH and AF, 7 had cirrhosis on biopsy (70.0%). Mean age of patients with biopsy-proven NASH was 53.7 ± 12.8 years and 37.1% were male. Patients with biopsy-proven NASH and AF were older (61.8 (standard deviation, 5.3 years) vs. 53.1 (12.6) years) and had a higher prevalence of hypertension (81.8% vs. 43.6% p=0.03), diabetes mellitus (81.8% vs. 45.4% p=0.03), heart failure (54.5% vs. 8.8%, p<0.001) and cerebrovascular (27.3% vs. 2%, p<0.001), or vascular disease (54.5% vs. 13.2%, p=0.002), compared to those with NASH alone. Patients with biopsy-proven NASH and AF had more hospital visits (4.3 vs. 2.0, p=0.006) and longer hospital stays compared to those with NASH alone (11.1 vs. 4.5 days, p=0.002). Eight of the 10 patients had at least one hospitalization for cardiovascular-related events (Table 2). Two patients were hospitalized for gastrointestinal hemorrhage.

Documented therapy and stroke risk for the 10 biopsy-proven NASH with AF is shown in Table 3. Among this cohort, all patients had a CHA2DS2VASc score ≥ 2 indicating an annual stroke risk of 2.2% and thus an indication for anticoagulation.²² Patients 1 and 7 received low dose aspirin therapy instead of anticoagulation therapy for secondary prevention of stroke; there is not a documented explanation for this undertreatment. Patients 9 and 10 received therapy with direct-acting oral anticoagulants, and three patients received therapy with warfarin. Patient 6 did not receive anticoagulant therapy because of a history of bleeding arteriovenous malformations in the gastrointestinal tract and patient 8 had a history of bleeding esophageal varices. Patient 3 did not receive anticoagulation for unclear reasons. Thus, of the 10 patients in this cohort, 80% (n=8) were eligible for guideline-appropriate anticoagulation and only 62.5% (n=5) of eligible patients received anticoagulation therapy. Two patients were not receiving anticoagulation due to a history of recent bleeding.

Discussion:

In our large urban tertiary care center, the prevalence of AF among patients with NASH with mean age of 54 years was 4.6% and among patients <65 years old was 4.0%. In contrast, among patients <65 years old without NASH evaluated at our institution, the prevalence of AF was only 2.7%. The prevalence of AF in US adults < 65 years old is estimated to be 2% though it exceeds 9% for patients older than 65 years.¹⁹ Patients with NASH and AF had increased healthcare utilization manifested by higher rates of hospitalization and longer length of stay compared to the NASH cohort without AF. Importantly, only 62.5% of patients with biopsy-proven NASH and AF, all with a documented elevated stroke risk, were receiving guideline-directed therapy for AF aimed at reducing thromboembolic stroke risk. The literature discussing prescriber non-adherence to anticoagulation guidelines in AF is sparse and ranges from 20% to 60%, the rate of adherence observed in our study is slightly higher yet still indicates undertreatment.^{23–26}

Our findings are consistent with other studies, demonstrating an increased prevalence, as well as incidence, of AF in patients with NAFLD.^{10,11,27} There is growing epidemiologic evidence which establishes NAFLD as a risk factor for the development of AF, and studies cite a prevalence of AF between 10%–15% in patients with NAFLD.^{10,11,27} Coupled with the fact that NASH prevalence is increasing worldwide, it is reasonable to expect that the prevalence and potentially incidence of AF among patients with NASH will also increase in the future. Ongoing clinical and population-based studies are needed to fully document the burden of concurrent AF and NAFLD.

Adherence studies of anticoagulation therapy for AF alone reveal that despite clear guidelines, patient undertreatment and guideline non-adherence remain significant issues.^{32–34} This is evident in our cohort, as two patients were inappropriately prescribed antiplatelet therapy instead of anticoagulation therapy. Importantly, no studies, with the exception of the SPAF (Stroke Prevention in Atrial Fibrillation)-1 trial, show benefit for 325 milligrams of aspirin alone in preventing stroke among patients with AF.³⁵ As demonstrated in a high-quality meta-analysis including 29 randomized control trials testing antithrombotic therapies of > 12 weeks' duration among 28,044 patients, antiplatelets are less effective than anticoagulation for stroke risk reduction in nonvalvular AF and yet they have similar rates of overall bleeding.³⁶ Understanding the potentially magnified cardiovascular and thromboembolic risk among patients with NASH and concomitant AF, treatment with careful attention to disease-specific guidelines can improve outcomes by preventing thromboembolic events such as stroke.^{32,37,38}

Patients with NASH may be undertreated for primary prevention of stroke due to a concern for increased bleeding risk, particularly in cirrhosis. The ability to assess the balance between increased risk of bleeding and hypercoagulability in cirrhosis is complex. Many patients with AF in the setting of cirrhosis are hypercoagulable. However, the risk of bleeding complications while receiving anticoagulation therapy can dampen enthusiasm for the initiation of anticoagulation.³⁹ Additionally, there are not clear guidelines on how a history of bleeding or further decompensation should impact treatment.⁴⁰ Few studies have examined the safety of anticoagulation in cirrhosis specifically for the indication of AF, and

those that did demonstrated some benefit in stroke prevention in well-compensated cirrhosis with AF but increased bleeding risk in those with hepatic decompensation.^{39,41,42} In our study, 50% (n=5) of patients with NASH/NASH cirrhosis and concomitant AF were not receiving anticoagulation when it was medically indicated. Only two of these patients had a documented reason, i.e. bleeding events, for not receiving therapy. Of the seven patients with AF and NASH cirrhosis in our cohort, there were three patients with a documented history of gastric or esophageal varices receiving anticoagulation therapy, but these patients had well-compensated cirrhosis and low MELD scores.

The pathophysiologic mechanisms delineating how patients with NAFLD may have a propensity to develop AF are not well understood as outlined in a recent excellent review by Anstee and colleagues.⁴³ Shared risk factors, such as obesity, hypertension, and diabetes, make establishing a direct causative link between the two quite challenging.¹¹ Studies suggest that the insulin resistance, visceral obesity, and the inflammatory environment found in NAFLD may underlie the development of AF.^{11,44} Additionally, patients with NAFLD have alterations in cardiac structure which may predispose to AF development.⁴⁵ A number of studies have reported increased left atrial volume and size, left ventricular wall thickness and mass, and impaired diastolic function among persons with NAFLD, which are known risk factors for the development of AF.^{45–47} In a recent large population-based study of over 3000 black and white middle-aged adults with CT-diagnosed NAFLD, NAFLD was independently associated with subclinical myocardial remodeling and dysfunction independent of established heart failure risk factors.⁴⁵ Thus, it is plausible that early myocardial remodeling in the setting of NAFLD state coupled with the progressive inflammatory milieu of NASH may potentially alter cardiac metabolism and function, and thus predispose to the development of AF. The hypothesis that systemic factors rather than direct hepatic processes may underlie the association is supported by the epidemiologic observation that gamma glutamyl transpeptidase (GGT), a marker of both hepatocyte injury and systemic oxidative stress, is independently associated with incident AF, whereas aminotransferases, as markers of hepatocyte injury alone, have not been independently associated with incident AF.⁴⁸

Fibrosis itself may play a significant role in the development of cardiac remodeling and AF in NASH. A recent cross-sectional analysis from the population-based Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that early subclinical liver stiffness, a marker of possible fibrosis, as assessed by T1-mapping via magnetic resonance imaging is highly associated with prevalent AF independent of traditional AF risk factors.⁴⁹ T1-mapping-derived indices of liver stiffness were also correlated with cardiac structure and functional parameters including left ventricular hypertrophy, left atrial dysfunction, and myocardial fibrosis, findings that might partly explain the mechanisms for the association of liver fibrosis with AF. In addition, analysis from the Oulu Project Elucidating the Risk of Atherosclerosis (OPERA) study demonstrated that increasing liver stiffness, as measured by transient elastography, is associated with increased AF prevalence.⁵⁰ A significant portion of our cohort had advanced fibrosis by biopsy and thus the high prevalence of AF among NASH observed in our study may be mediated by the presence of fibrosis. Nevertheless, the mechanisms of the association of liver fibrosis with AF and heart failure are yet to be elucidated.

Strengths and Limitations:

Our study has several strengths. First, our findings support recent publications which define AF as highly prevalent in the NAFLD population by extending this finding to the NASH subpopulation, who arguably is at higher risk for both liver and cardiovascular-related complications related to AF. It is to date the only study to assess anticoagulation use in patients with concurrent AF and NASH, highlighting the need for improved understanding of barriers to adherence to treatment guidelines and the safety of anticoagulation treatment in this particular patient population. There are several limitations of our study that warrant mention. The main limitation is the small size of the biopsy-proven NASH and AF group. While our biopsy-proven patient population is small, prevalence estimates were similar when ICD-9 codes were used to define NAFLD/NASH. In addition, pathology slides from all patients were not available to re-review and so we do not have NAFLD activity scores (NAS) available on all patients, nor was the degree of fibrosis quantified with each pathology read. The small sample size may underestimate the association between AF and NASH as there likely was a significant proportion of patients with likely NASH who did not receive a liver biopsy for diagnosis. Additionally, we relied upon ICD-9 coding to capture patients with a diagnosis of AF, but we may have underestimated the true prevalence of AF in this patient population as some patients may have paroxysmal AF which was undiagnosed. In addition, the increased number of hospital visits among patients with NASH and AF may have led to increased diagnosis of AF due to increased encounters with the healthcare system. A key reference population for AF prevalence was obtained from published data in the general US population and may not be well-matched to our cohort, as our patients had a high comorbidity burden and sought care in a tertiary center. However, we attempted to address this limitation by including reference data for patients without NASH and who also had AF at our institution. We were not able, however, to perform a matched propensity analysis for healthcare utilization in the AF alone versus NASH and AF cohorts. Finally, we are unable to link adherence to guideline-based anticoagulation management in NASH and AF to hard clinical outcomes, in particular stroke and CVD mortality, due to the small sample size. However, reporting of our single center experience provides a baseline metric for which we, and others, can use to target quality improvement measures to assess outcomes associated with guideline-based therapy and ultimately improve care and outcomes in the high-CVD risk NASH population.

Conclusions:

AF prevalence is two-fold higher in patients with NASH and NASH cirrhosis compared to the general population. Patients with concurrent NASH and AF have a high burden of stroke, heart failure, diabetes, and healthcare utilization. Nearly 40% of patients with NASH and AF do not receive guideline-recommended anticoagulation for stroke risk reduction based on the CHA2DS2VASc score. Future studies are needed to identify at risk patients with NASH and AF, and to understand barriers, safety and clinical outcomes related to guideline-based management in the high-cardiovascular risk growing NASH population.

Abbreviations:

CVD	Cardiovascular disease
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
AF	Atrial fibrillation
BMI	body mass index
SHIP	Study of Health in Pomerania
ICD-9-CM	International Classification of Diseases, the 9 th Revision, Clinical Modification
ICU	intensive care unit
MESA	Multi-Ethnic Study of Atherosclerosis; renin-angiotensin-aldosterone system
NAS	NAFLD activity score

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Figure 1.

Prevalence rates of atrial fibrillation in persons < 65 years old according to disease status.

General population estimate is derived from previously published data.

Table 1.

Characteristics of biopsy-proven NASH patients with and without atrial fibrillation (N=215) Mean (SD) or n (%)

	NASH alone (n=205)	NASH + AF (n=10)	P value*
Age, years, mean (SD)	53.1 (12.6)	61.8 (15.3)	0.03
<65 years	169 (82.4)	7 (63.6)	
65-75 years	29 (14.1)	2 (18.2)	
>= 75 years	7 (3.4)	3 (18.2)	
Gender, n (%)			
Male	76 (37.1)	5 (45.5)	0.81
Female	129 (62.9)	6 (54.5)	
Body mass index, kg/m ²	32.7 (7.4)	30.05 (8.6)	0.26
Obesity	117 (61.6)	5 (45.5)	0.35
Spontaneous Bacterial Peritonitis	2 (1.0)	0 (0.0)	>0.999
Hepatic Encephalopathy	13 (6.3)	2 (18.2)	0.17
Portal Venous Thrombosis	7 (3.4)	0 (0.0)	>0.999
Esophageal/Gastric Varices	37 (18.0)	4 (36.4)	0.23
Hepatocellular carcinoma	7 (3.4)	0 (0.0)	>0.999
Hepatopulmonary Syndrome	1 (0.5)	0 (0.0)	>0.999
Hepatorenal Syndrome	1 (0.5)	0 (0.0)	>0.999
Family history of coronary artery disease	7 (3.4)	0 (0.0)	>0.999
Diabetes Mellitus	93 (45.4)	9 (81.8)	0.03
Hypertension	95 (46.3)	9 (81.8)	0.03
Hyperlipidemia	83 (40.5)	8 (72.7)	0.07
Stroke/TIA	4 (2.0)	3 (27.3)	<0.001
Atherosclerotic disease**	27 (13.2)	6 (54.5)	0.002
Congestive heart failure	18 (8.8)	6 (54.5)	<0.001
Anti-hypertensive medication use	0 (0.0)	2 (18.2)	<0.001
Beta-blocker medication use	0 (0.0)	1 (9.1)	0.05

* t-test, chi square or fisher exact test for comparisons between NASH alone and NASH+AF

** Atherosclerotic disease is defined as history of myocardial infarction, aortic plaques, peripheral arterial disease.

Abbreviations: AF, atrial fibrillation; SD, standard deviation; NASH, nonalcoholic steatohepatitis; TIA, transient ischemic attack

Table 2.

Indications for hospitalization

	Total number of hospitalizations	Count of primary indication for hospitalization						
		Liver disease	Gastrointestinal hemorrhage	Cardiovascular disease	Renal disease	Pulmonary disease	Infectious disease	Other [*]
Patient 1	1	0	0	1	0	0	0	1
Patient 2	2	1	0	0	0	0	0	1
Patient 3	5	0	0	4	0	0	0	2
Patient 4	>10	+ [#]	0	+	+	+	+	+
Patient 5	3	1	0	1	0	0	0	1
Patient 6	10	2	2	2	1	3	1	2
Patient 7	5	0	0	3	1	0	2	0
Patient 8	2	0	0	1	1	0	1	0
Patient 9	2	1	0	0	0	0	0	2
Patient 10	4	3	1	1	3	0	0	0

^{*} Hospitalizations for planned procedures, ablations/cardioversions.

[#] The patient had numerous hospitalizations, many which exceeded a few weeks in duration, over the time period of this study with the majority of discharge diagnoses being liver-related

Table 3.

Characteristics of patients with biopsy-proven NASH and AF

Patient #	Cirrhosis	CTP class	MELD score	CHA2DS2VASc	CHF	AC	Varices
1	No	A	7	5	No	Yes(^{1, #})	No
2	Yes	B	23	4	No	Yes ([*])	No
3	No	A	6	5	No	No	No
4	No	B	13	5	No	Yes ([*])	No
5	Yes	C	20	4	HFpEF	Yes ([*])	No
6	Yes	A	8	7	HFrEF	No	No
7	Yes	A	22	5	No	Yes(^{2, #})	No
8	Yes	B	16	3	HFrEF, HFpEF	No	Yes
9	yes	A	7	4	No	Yes (^{&})	Yes
10	yes	B	15	5	no	Yes ([%])	Yes

¹ On aspirin for secondary CVA prevention² Briefly on anticoagulation, now on dual antiplatelet therapy^{*} warfarin[#] aspirin[%] apixaban[&] rivaroxaban

Abbreviations: CTP (Child Turcot Pugh), MELD (Model for End Stage Liver Disease), CHF (congestive heart failure), EF (ejection fraction), AC (anticoagulation), HFpEF (heart failure with preserved ejection fraction), HFrEF (heart failure with reduced ejection fraction)