Patients with atrial fibrillation and diabetes mellitus affected by nonalcoholic fatty liver disease have a greater risk of mortality and worse clinical outcomes

Leonid Khokhlov[a], Bekure Siraw[b], Mehnaaz Ali[a], Fatima Hussain[a], Amanda Brown[c] and Kamal Shemisa[a]

Background **Nonalcoholic fatty liver disease (NAFLD) is associated with several adverse clinical outcomes. In this study, we assessed the association between NAFLD and several clinical outcome measures in patients with diabetes mellitus (DM) and atrial fibrillation (AF).**

Methods **We queried the National Inpatient Sample (NIS) between 2016 and 2019 for adult patients who were hospitalized with DM and AF. NAFLD was the independent variable. The primary outcome was inpatient mortality. The secondary outcomes were cardiogenic shock, cardiac arrest, gastrointestinal bleeding (GIB), invasive mechanical ventilation, length of stay, and total hospital charges. A multivariable logistic regression model was used to estimate odds ratios with a 95% confidence interval (CI) and a *P* value of less than 0.05 was considered significant.**

Results **There were 6 723 293 hospitalizations with AF and DM and 253 639 (3.7%) had NAFLD. NAFLD and non-NAFLD cohorts had a mean age of 70.4 vs. 73.8 years, respectively. Overall, 55.6% were male and 73.8% were White. NAFLD was found to be significantly associated with in-hospital mortality [adjusted odds ratio (AOR), 4.2; 95% CI, 4.08–4.32], cardiogenic shock (AOR, 4.78; 95% CI, 4.59–4.98), cardiac arrest (AOR, 3.43; 95% CI, 3.27–3.59), GIB (AOR, 1.92; 95% CI, 1.86–1.98), length of stay, and total hospital charges.**

Conclusion **In patients with AF and DM patients, the presence of NAFLD was associated with significantly worse clinical outcomes and higher resource utilization. Adverse cardiovascular events were common as well as GIB. Screening and prevention strategies modifying the risk and disease severity of NAFLD are needed.**

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[a]Department of Internal Medicine, Good Samaritan Hospital, TriHealth, Cincinnati, Ohio, [b]Department of Internal Medicine, Ascension Saint Joseph Hospital, Chicago, Illinois and [c]Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio, USA

Correspondence to Leonid Khokhlov, MD, Department of Internal Medicine, Good Samaritan Hospital, TriHealth, Cincinnati, OH 45202, USA
E-mail: leonkhokhlov@gmail.com

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Background

Nonalcoholic fatty liver disease (NAFLD) is defined by the presence of hepatic steatosis either on imaging or histology in the absence of causes for secondary fat accumulation like significant alcohol consumption, toxic exposure, use of steatogenic medications, or hereditary disorders [1]. NAFLD can be further histologically classified into nonalcoholic fatty liver, nonalcoholic steatohepatitis (NASH), and nonalcoholic cirrhosis. Nonalcoholic fatty liver is defined as the presence of hepatic steatosis with no evidence of hepatocyte injury, whereas NASH is defined as the presence of hepatic steatosis and hepatocyte inflammation/injury with or without fibrosis [1]. The pathogenesis of NAFLD involves a 'three-hit' process involving steatosis, lipotoxicity, and inflammation [2].

The prevalence of NAFLD in the USA ranges widely from 13 to 55% based on different observational analyses [3–6]. A study from a nationally representative sample showed that the prevalence of NAFLD has increased from 29.5% in 1999–2000 to 40.3% in 2015–2016 [5]. NAFLD prevalence was reported to be highest in Hispanics, intermediate in Whites, and lowest in Blacks [3,6]. The overall incidence rate of NAFLD increases with increasing age and is higher in males than females [7]. Over 64 million people are projected to have NAFLD in the coming decade, with annual direct medical costs of about $103 billion ($1613 per patient) [8]. NAFLD has been associated with an increased risk of myocardial infarction, ischemic stroke, and heart failure which are major causes of in-hospital mortality [9].

The global prevalence of NAFLD and NASH among patients with T2DM is 55.5 and 37%, respectively [10]. Over the next 20 years, NASH with T2DM is expected to account for 65 000 transplants, 1.37 million cardiovascular-related deaths, and 812 000 liver-related

deaths [11]. There is a close bidirectional relationship between NAFLD and type 2 diabetes mellitus (T2DM); NAFLD increases the risk for T2DM and its cardiovascular complications [12]. NAFLD-affected population has an increased risk of development of T2DM and hypertension: 11.7 and 7.99 times higher, respectively [13]. In patients with NAFLD, T2DM is associated with a three-fold increase in all-cause and cardiovascular mortality [13,14].

Patients with NAFLD have been shown to have a two-fold increased risk of incident atrial fibrillation (AF) [15]. In patients with AF, advanced age, heart failure, previous cardiac, and cerebrovascular events use of direct oral anticoagulants, and female sex are associated with increased risk of adverse cardiovascular events. In contrast, the use of direct oral anticoagulants was found to be associated with decreased risk [16].

In this study, we assessed the association between NAFLD and several clinical outcome measures including inpatient mortality, cardiogenic shock, cardiac arrest, gastrointestinal bleeding (GIB), invasive mechanical ventilation, resource utilization, and length of stay (LOS) in patients with diabetes mellitus (DM) and AF.

Methods

Study design and population

A retrospective cohort study was conducted using the National Inpatient Sample (NIS) database provided by the Healthcare Cost and Utilization Project (HCUP) from January 2016 to December 2019. This database stores deidentified information about individual hospitalizations, including demographic characteristics, diagnoses, and procedures in the form of the *International Classification of Diseases, 10th Revision* (ICD-10) codes. Internal validity of the database is maintained by utilization of annual quality assessments, and external validity is assessed and kept by comparison with the National Hospital Discharge Survey from the National Center for Health Statistics, the American Hospital Association Annual Survey Database, and the MedPAR inpatient data from the Centers for Medicare and Medicaid Services.

Study variables

We used the following codes to identify AF: I48.0 (paroxysmal AF), I48.1 (persistent AF), I48.2 (chronic AF), I48.91 (unspecified AF); codes used for DM: E10 (T1DM), E11 (T2DM), E13 (unspecified DM); codes used for NAFLD: K72 (hepatic failure), K73 (chronic hepatitis), K74 (fibrosis and cirrhosis), and K75 (other inflammatory liver diseases). In the codes for NAFLD given above, toxic, alcoholic, viral, and congenital subtypes were excluded per ICD-10 coding parameters.

The primary outcome was all-cause in-hospital mortality. The secondary outcomes were cardiogenic shock, cardiac arrest, GIB, invasive mechanical ventilation, LOS, and total hospital charge.

Statistical analysis

Continuous variables were summarized using means and SDs and compared using a *t*-test. Categorical variables were summarized using proportions and compared using the chi-square test. A multivariate logistic regression model with adjustment for age, sex, race, Charlson Comorbidity Index score, and comorbid chronic medical conditions (obesity, dyslipidemia, hypertension, peripheral vascular disease, stroke, anemia, and chronic respiratory failure) was used for the following outcome variables: death during hospitalization, cardiogenic shock, cardiac arrest, GIB, and invasive mechanical ventilation. A multivariate Poisson regression model with adjustment for inflation between 2016 and 2019 using the Medical Expenditure Panel Survey [17] and adjustment for basic characteristics and chronic comorbidities (similar to the adjustment described above for clinical outcomes) was used for the LOS and total hospital charge. Those variables which were found to have associations with outcome variables were selected to be included in the final multivariate regression model using a P value cutoff of 0.2 (also known as the univariate screening method). The output of all tests was reported with a 95% confidence interval (CI) at a 0.05 level of significance. Data analysis was performed with the use of STATA 17.0 software (StataCorp LLC, Texas, USA) [18].

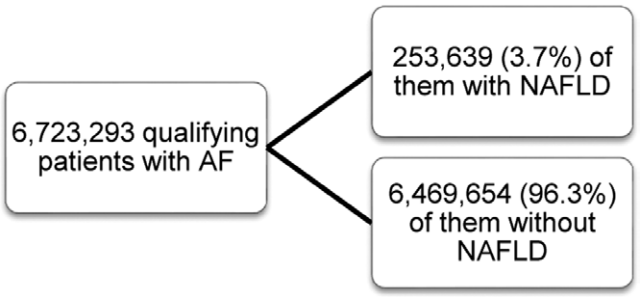
Results

There were 6 723 293 hospitalizations of patients with concomitant diagnoses of AF and T2DM (Fig. 1). Of those, 253 639 (3.7%) had NAFLD. NAFLD and non-NAFLD cohorts had a mean age of 70.4 vs. 73.8 years; males 57.2 vs. 55.6%; Caucasians 70.5 vs. 73.9%; hypertension 20.3 vs. 29.2%; heart failure 61.4 vs. 56%; acute coronary syndrome 12.2 vs. 9.4%; chronic kidney disease 53.4% vs. 45.2%; acute kidney disease 47.1 vs. 30.4%; obesity 26.9% vs. 27.1%; dyslipidemia 49.8 vs. 61.9%; anemia 24.8 vs. 19.2%; history of myocardial infarction 10.9 vs. 13.3%; stroke 2.4 vs. 4.1%, chronic obstructive pulmonary disease 28.8% vs. 31.1%; and alcohol use 5.2 vs. 2.2%, respectively (Table 1).

Primary outcomes

The incidence of in-hospital mortality was 14.8 and 4.0% in the group with and without NAFLD, respectively. NAFLD was significantly associated with increased odds of in-hospital mortality. After adjusting for age, sex, race, Charlson Comorbidity Index score, and comorbid chronic medical conditions (obesity, dyslipidemia, hypertension, peripheral vascular disease, stroke, anemia, and chronic respiratory failure) this association remained statistically

Fig. 1



Flow diagram of patient selection. AF, atrial fibrillation; NAFLD, nonalcoholic fatty liver disease.

Table 1 Characteristics in patients with atrial fibrillation and diabetes mellitus

Characteristics	AF and DM without NAFLD	AF and DM with NAFLD	*P* value
Number	6 469 653 (96.3%)	253 639 (3.7%)	
Males, %	55.6	57.2	< 0.001
Mean age, years	73.8	70.4	< 0.001
Race/ethnicity, %			< 0.001
White	73.9	70.5	
Black	11.2	9.9	
Other	14.8	19.5	
Comorbidities, %			
Obesity	27.1	26.9	0.34
Dyslipidemia	61.9	49.8	< 0.001
HTN	29.2	20.3	< 0.001
Pulmonary HTN	11.7	15.9	< 0.001
Chronic AC	37.8	25.7	< 0.001
HF, all	56.0	61.4	< 0.001
HFrEF	23.4	27.7	< 0.001
DKA	0.9	1.4	< 0.001
Anemia	19.2	24.8	< 0.001
ACS	9.4	12.2	< 0.001
STEMI	0.7	1.4	< 0.001
MI, previous	13.3	10.9	< 0.001
Long QT syndrome	0.7	1.0	< 0.001
PE	4.1	3.2	< 0.001
PVD	4.6	3.8	< 0.001
AKI	30.4	47.1	< 0.001
CKD	45.2	53.4	< 0.001
Stroke	4.1	2.4	< 0.001
COPD	31.1	28.8	< 0.001
Nicotine use	9.2	9.7	< 0.001
Alcohol use	2.2	5.2	< 0.001

AC, anticoagulation; ACS, acute coronary syndrome; AF, atrial fibrillation; AKI, acute kidney injury; CKD, chronic kidney injury; COPD, chronic obstructive pulmonary disease; DKA, diabetic ketoacidosis; DM, diabetes mellitus; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HTN, hypertension; MI, myocardial infarction; NAFLD, nonalcoholic fatty liver disease; PE, pulmonary embolism; PVD, peripheral vascular disease; STEMI, ST elevation myocardial infarction.

significant [adjusted odds ratio (AOR), 4.2; 95% CI, 4.08–4.32].

Secondary outcomes

The incidence of cardiogenic shock (7.2 vs. 1.3%, $P < 0.001$), cardiac arrest (4.7 vs. 1.2%, $P < 0.001$), GIB (10.4 vs. 5.4%, $P < 0.001$), and invasive mechanical ventilation (13.2 vs. 4.1%, $P < 0.001$) were found to be significantly higher in patients with NAFLD than those without. After adjustments for age, sex, race, Charlson Comorbidity Index score, and comorbid chronic medical conditions (obesity, dyslipidemia, hypertension, peripheral vascular disease, stroke, anemia, and chronic respiratory failure), NAFLD was found to be significantly associated with increased odds of cardiogenic shock (AOR, 4.78; 95% CI, 4.59–4.98), cardiac arrest (AOR, 3.43; 95% CI, 3.27–3.59), GIB (AOR, 1.92; 95% CI, 1.86–1.98), and invasive mechanical ventilation (AOR, 3.22; 95% CI, 3.13–3.32).

The mean LOS was longer in patients with NAFLD. (7.9 vs. 6 days, $P < 0.001$). NAFLD was found to be significantly associated with increased mean LOS (adjusted risk ratio, 1.23; 95% CI, 1.22–1.24). Table 2 summarizes the outputs of the regression models with AOR and adjusted risk ratio estimates.

The mean total hospital charge was 77 273 USD (SD = 1432) and 52 073 USD (SD = 591) in patients with and without NAFLD, respectively. After adjustment for inflation, NAFLD was found to be significantly associated with increased total hospital charges. ($P < 0.001$).

Discussion

The aim of this study was to determine the association between NAFLD and clinical outcome measures of patients with DM and AF. Patients admitted for NAFLD were specifically associated with an increased risk of in-hospital mortality, cardiogenic shock, cardiac arrest, GIB, invasive mechanical ventilation, prolonged LOS, and higher total hospital charges (Table 2 and Fig. 2).

Patients with preexisting DM and AF were more likely to have heart failure, pulmonary hypertension, acute coronary syndrome, acute and chronic kidney disease, and anemia.

The results of our study demonstrate the association between NAFLD and adverse outcomes in patients with DM and AF. Patients admitted to the hospital for NAFLD had three times higher inpatient mortality compared with patients not hospitalized for NAFLD. The NAFLD cohort had higher odds of having adverse cardiac events including 4.8 higher odds of cardiogenic shock and 3.4 higher odds of cardiac arrest. In addition, the NAFLD hospitalized patients had 1.92 higher odds of GIB and 3.2 higher odds of undergoing invasive mechanical ventilation. Hospitalized NAFLD patients were associated with a significant increase in length of hospital stay and total hospital charge, showing a 1.23 increase in mean LOS and an increase in the mean total hospital charge of $77 273 vs. $52 073 compared with patients without NAFLD.

The study analysis confirms the hypothesis that patients suffering from NAFLD with underlying DM and AF have higher inpatient mortality. This study is one of very

Table 2 Clinical outcomes

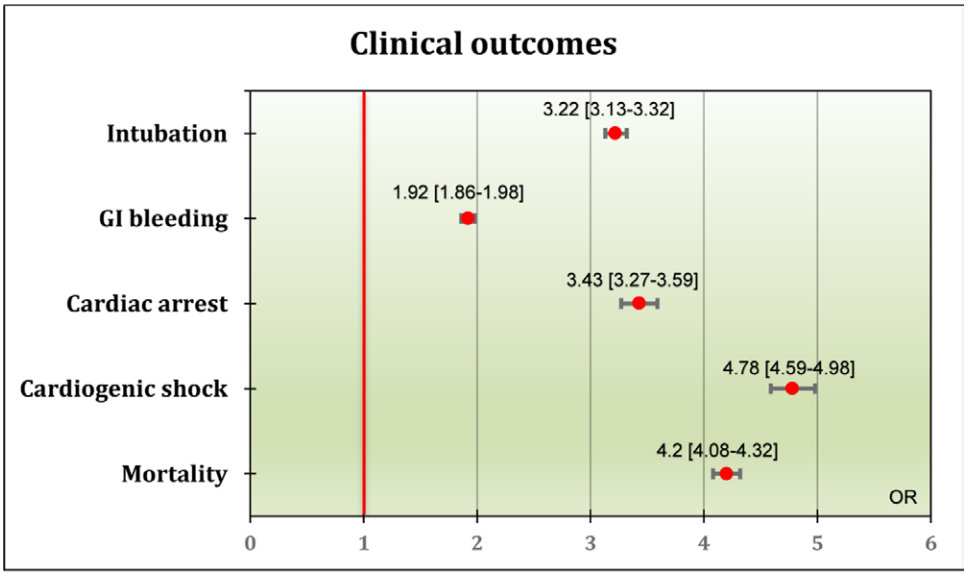
Outcome	AF and DM without NAFLD	AF and DM with NAFLD	OR (95% CI)[a]	IRR (95% CI)[a]	*P* value[a]
Primary					
Death during hospitalization	261 024 (4.0%)	37 749 (14.8%)	4.2 (4.08–4.32)	NA	< 0.001
Secondary					
Cardiogenic shock	85 635 (1.3%)	18 345 (7.2%)	4.78 (4.59–4.98)	NA	< 0.001
Cardiac arrest	83 010 (1.2%)	12 150 (4.7%)	3.43 (3.27–3.59)	NA	< 0.001
Gastrointestinal bleeding	353 614 (5.4%)	26 510 (10.4%)	1.92 (1.86–1.98)	NA	< 0.001
Invasive mechanical ventilation	267 375 (4.1%)	33 719 (13.2%)	3.22 (3.13–3.32)	NA	< 0.001
LOS, mean (SD) (days)	6.0 (0.01)	7.9 (0.05)	NA	1.23 (1.22–1.24)	< 0.001
Total charge, mean (SD) (USD)[b]	52 073 (591)	77 273 (1432)	NA	1.34 (1.31–1.37)	< 0.001

AF, atrial fibrillation; CI, confidence interval; DM, diabetes mellitus; IRR, incidence rate ratio; LOS, length of stay; NAFLD, nonalcoholic fatty liver disease; OR, odds ratio; USD, US dollar.

[a]Adjusted for age, sex, race, Charlson Comorbidity Index score, obesity, AF, DM, dyslipidemia, hypertension, peripheral vascular disease, stroke, anemia, chronic respiratory failure.

[b]Adjusted for inflation 2016–2019 using Medical Expenditure Panel Survey.

Fig. 2



Plot demonstrating OR for clinical outcomes in patients with nonalcoholic fatty liver disease. GI, gastrointestinal; OR, odds ratio.

few studies evaluating the clinical outcomes of NAFLD patients with coexisting DM and AF. Data from the retrospective cohort study by Wild *et al.* [19] demonstrates that NAFLD is associated with a 60% higher risk of all-cause mortality in patients with DM. In addition, DM is associated with an increased risk of all-cause and cardiovascular mortality in patients with NAFLD [13,20,21]. Although several studies have shown that NAFLD is associated with an increased risk of incident AF, evidence regarding the risk of mortality of NAFLD in patients with AF is limited [15,22].

Cardiogenic shock and cardiac arrest are critical cardiac complications that can significantly impact patient outcomes. Our study demonstrated a significant association between NAFLD and an increased risk of cardiogenic shock and cardiac arrest in patients with DM and AF. NAFLD has been shown to be associated with an increased risk of ischemic heart disease and heart failure, which is in turn associated with increased risk of both cardiogenic shock and cardiac arrest [23,24]. Similar pathogenic factors leading to NAFLD like insulin resistance and inflammation affect the heart and raise the risk of both AF and HF. Targher and colleagues reported that patients with NAFLD have a significantly prolonged heart rate-corrected QT in patients with DM. This appears to be related to the greater risk for QRS conduction delay in DM, abnormal electrolyte levels, and the delayed metabolism of medications that raise the QT. QT prolongation is associated with an increased risk of Torsades-de-Pointes and cardiac arrest [25]. Similarly, Minhas *et al.* [26] reported that NAFLD is associated with an increased risk of cardiogenic shock, pressor use, and cardiac arrest in patients with heart failure regardless of the ejection fraction.

GIB is another important adverse outcome of NAFLD in patients with DM and AF. Our finding of increased risk of GI bleeding in patients with NAFLD is consistent with findings from prior studies. NAFLD has been shown to be associated with an increased risk of variceal bleeding with increasing fibrotic stages [27]. Liver dysfunction, portal hypertension, and coagulation abnormalities contribute to the increased risk of GIB in NAFLD patients [28]. Concomitant treatment with anticoagulants and antiplatelet medications further raises the risk of bleeding.

Our study also showed an increased risk of invasive mechanical ventilation associated with NAFLD. This observed increased need for invasive mechanical ventilation may be attributed to several factors. Both prevalent obstructive sleep apnea and HF can lead to respiratory compromise and the need for ventilatory support [29]. In addition, the systemic inflammation and metabolic abnormalities associated with NAFLD may contribute to respiratory distress and the requirement for invasive mechanical ventilation. In a study by Gjurašin *et al*. [30], NAFLD was found to be associated with an increased risk of invasive mechanical ventilation in patients admitted with community-acquired pneumonia.

The prolonged LOS and higher total hospital charges observed in NAFLD patients with DM and AF reflect the economic burden and resource utilization associated with this condition. NAFLD is a complex disease with multiple comorbidities that require comprehensive management, leading to increased healthcare costs. Our findings of significantly longer hospital stays and higher healthcare costs in NAFLD patients compared with those without NAFLD are consistent with findings from previous studies [31].

Limitations

It is important to acknowledge the limitations of our study. First, the retrospective nature of the analysis and the use of electronic health record data may introduce bias and confounders that were unaccounted for in our analysis. Second, the study did not account for the severity of NAFLD or the specific treatment strategies employed, which could influence the outcomes observed. Last, ICD codes were used to identify patients with NAFLD which may not be accurate in identifying patients with true NAFLD based on the guideline-based diagnostic criteria which may lead to nondifferential misclassification of our exposure variable.

Conclusion

Our study showed that NAFLD in patients with AF and DM is associated with an increased risk of in-hospital mortality, adverse clinical outcomes, and resource utilization. Future prospective studies with more detailed clinical data are needed to further elucidate the association between NAFLD and adverse outcomes in patients with DM and AF. Further research is also necessary to understand the extent of the clinical implications of NAFLD in other subgroups of hospitalized patients.

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