Association Between Metabolic Dysfunction-Associated Fatty Liver Disease and Supraventricular and Ventricular Tachyarrhythmias in Patients with Type 2 Diabetes

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ABSTRACT

Background: Currently, it remains uncertain whether metabolic dysfunction-associated fatty liver disease (MAFLD) is associated with increased risk of supraventricular and ventricular tachyarrhythmias in people with type 2 diabetes mellitus (T2DM).

Methods: We retrospectively examined the data of 367 ambulatory patients with T2DM who underwent 24-hour Holter monitoring between 2015 and 2022 for clinical indications, and who did not have pre-existing permanent atrial fibrillation (AF), kidney failure or known liver diseases. Paroxysmal supraventricular tachycardia (PSVT), paroxysmal AF and episodes of ventricular tachyarrhythmias (i.e., presence of ventricular tachycardia, >30 premature ventricular complexes per hour, or both) were recorded. The presence and severity of MAFLD was diagnosed by ultrasonography and fibrosis-4 (FIB-4) index.

Results: Patients with T2DM who had MAFLD (n=238) had a significantly greater prevalence of PSVT (51.7% vs. 38.8%), paroxysmal AF (6.3% vs. 1.3%) and combined ventricular tachyarrhythmias (31.9% vs. 20.2%) compared to their counterparts without MAFLD (n=129). MAFLD was significantly associated with a greater than two-fold risk of having PSVT (adjusted-odds ratio [OR] 2.04, 95% confidence interval 1.04-4.00) or ventricular tachyarrhythmias (adjusted-OR 2.44, 95%CI 1.16-5.11), after adjusting for age, sex, smoking, **alcohol intake**, diabetes-related factors, comorbidities, medication use and left ventricular ejection fraction on echocardiography. The risk of supraventricular and ventricular tachyarrhythmias was even greater amongst patients with MAFLD and FIB-4 ≥1.3.

Conclusions: In ambulatory patients with T2DM, the presence and severity of fatty liver disease was strongly associated with an increased risk of supraventricular and ventricular arrhythmias on 24-hour Holter monitoring.

Introduction

Nonalcoholic fatty liver disease (NAFLD) has become a public health problem worldwide, affecting up to a third of world's adults [1], and up to ~70% of patients with type 2 diabetes mellitus (T2DM) [2]. NAFLD is a "multisystem" disease that is not only associated with liver-related complications but is also associated with adverse cardiovascular events and other extrahepatic complications [3-5]. Cardiovascular disease (CVD) is the leading cause of mortality in people with NAFLD [3], and accumulating evidence suggests that NAFLD can also confer an increased risk of cardiomyopathy [6, 7]. Various forms of cardiac disease have been found in NAFLD and these include cardiac remodeling and hypertrophy (leading to new-onset heart failure), cardiac valvular calcification, arrhythmias (mainly permanent atrial fibrillation) and certain cardiac conduction defects (mainly right bundle branch block or left anterior hemiblock), regardless of the presence or absence of obesity, T2DM or metabolic syndrome [6, 7].

Recently, based on the intimate relationship between NAFLD and metabolic dysfunction, a panel of international experts has proposed a change of terminology from NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) [8]. The diagnosis of MAFLD can entertain the presence of fatty liver *plus* at least one of the following three metabolic risk abnormalities, including T2DM, overweight/obesity, or evidence of metabolic syndrome features in lean individuals who do not have T2DM [8]. Hence, MAFLD diagnosis does not require the exclusion of excessive alcohol consumption and may also coexist with other chronic liver diseases [9, 10].

However, irrespective of the proposed name change from NAFLD to MAFLD, it is important to underline that there is currently little information regarding the association between MAFLD and the risk of supraventricular and ventricular tachyarrhythmias on 24-hour Holter monitoring. Recognition of this association has important clinical implications, because it might contribute to explain the increased CVD risk observed in people with MAFLD.

Therefore, the aim of this cross-sectional study was to evaluate the association between the presence and severity of MAFLD (assessed by liver ultrasonography and Fibrosis-4 [FIB-4] index, i.e., a widely used non-invasive test for advanced fibrosis) and the risk of supraventricular and ventricular tachyarrhythmias in patients with T2DM, who underwent a clinically indicated 24-hour Holter monitoring.

Materials and methods

Patients

We retrospectively retrieved the electronic records of individuals with known T2DM, who regularly attended our diabetes outpatient service and who had undergone initial 24-hour Holter monitoring at our Cardiology outpatient service between January 2015 and June 2022 for clinical indications. Clinical indications included baseline electrocardiographic abnormalities, palpitations, presyncope, syncope, chest pain, or presence of multiple cardiovascular risk factors.

From an initially selected sample of 416 outpatients with established T2DM, who had undergone initial 24-hour Holter monitoring, we excluded 49 outpatients from analyses for the following reasons: (1) outpatients with permanent atrial fibrillation (n=2); (2) those with a pacemaker or implantable cardioverter defibrillator (n=2); (3) those with missing data for liver ultrasonography and FIB-4 index (n=36); and (4) those with documented history of primary hyperthyroidism, cancer, chronic kidney disease stage 5 (defined as either estimated GFR <15 mL/min/1.73 m^2 or chronic dialysis), alcohol abuse or cirrhosis of any etiology (n=9). As a result of these exclusion criteria, a total of 367 outpatients with T2DM (217 men and 150 women; median duration of diabetes 10 years; mean (±SD) age 72±10 years, mean HbA1c 7.3±1.3%) were included in the final analysis.

The local ethics committee approved the study protocol. The ethics committee exempted our research from the need for informed consent from participants, because we only accessed retrospectively a de-identified database for the purpose of data analysis.

Clinical and Laboratory Data

Body mass index (BMI) was calculated by dividing weight (in kilograms) by height (in square meters). Blood pressure was measured with a mercury sphygmomanometer using an appropriate cuff size after the subject had been seated quietly for at least 5 min. Subjects were considered as having arterial hypertension if their blood pressure was ≥140/90 mmHg or if they were taking any anti-hypertensive medications. Information about smoking history, daily alcohol consumption and use of medications (including beta-blockers and anti-arrhythmic agents) was also recorded from all participants.

Venous blood samples were drawn in the morning after an overnight fast. Complete blood count, serum liver enzymes, glucose, lipids, creatinine, electrolytes, thyroid stimulating hormone (TSH) and other biochemical blood parameters were measured using standard laboratory procedures at the Central Laboratory of our hospital. LDL-cholesterol was calculated using the Friedewald's equation. Hemoglobin A1c (HbA1c) was measured using the high-performance liquid chromatography analyzer Tosoh-G7 (Tosoh Bioscience Inc., Tokyo, Japan). The estimated glomerular filtration rate (e-GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equation [11]. Albuminuria was measured using an immuno-nephelometric method on a morning spot urine sample and expressed as the albumin-to-creatinine ratio. Abnormal albuminuria was defined as a urinary albumin-to-creatinine ratio ≥30 mg/g. Presence of chronic kidney disease (CKD) stage ≥3 was defined as an e-GFR$_{CKD-EPI}$ <60 mL/min/1.73 m^2. The presence of ischemic heart disease was defined as a documented history of myocardial infarction, angina pectoris, or coronary revascularization procedures. Valvular heart disease was defined as described in the medical records, including diagnostic symptoms and echocardiogram results. The presence of chronic obstructive pulmonary disease (COPD) was confirmed by reviewing medical records, including diagnostic symptoms and the results of lung function tests.

Holter Monitoring, Echocardiography, and Liver Ultrasonography

All 24-hour Holter monitoring, conventional echocardiography and liver ultrasonography were performed at our institution. Experienced Cardiologists, who were not aware of whether a patient had MAFLD or not, analyzed the 24-hour Holter monitoring recordings (Seer Light-DC3V Compact Digital Holter; GE Healthcare). The number of atrial premature complexes (APCs), the mean hourly APC number, the number of episodes of paroxysmal supraventricular tachycardia (PSVT) (which refers to rapid heart rates of sudden onset originating above the His-Purkinje system and resulting from either macro-reentry circuits or abnormal automaticity [12]), as well as the number of episodes of paroxysmal atrial fibrillation (AF) were recorded for all participants. The number of premature ventricular complexes (PVCs), the mean hourly PVC number, and the number of sustained or non-sustained ventricular tachycardia (VT) episodes were also recorded. In particular, VT was defined as three or more PVC beats with a mean R-R interval length of <600 ms and was sustained if it lasted >30 s, produced syncope, cardiac arrest or required cardioversion [13]. Experienced Cardiologists also performed a conventional echocardiography (Vivid 7; GE Vingmed, Horten, Norway) in a subset

of patients (n=244). Echocardiography was used to measure left ventricular (LV) ejection fraction, according to standard criteria [13].

In this study, based on the newly proposed definition of MAFLD [8], this condition was diagnosed by the presence of hepatic steatosis on ultrasonography. Experienced Radiologists, who were blinded to participants' clinical details, performed liver ultrasonography in all patients. Hepatic steatosis was diagnosed based on characteristic ultrasonographic features, such as diffuse hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualization of the intrahepatic vessel borders and diaphragm [14]. Ultrasonography has a good accuracy for detecting mild and moderate hepatic steatosis [15, 16]. A semiquantitative ultrasonographic scoring of steatosis severity was not available. We also calculated the fibrosis (FIB)-4 index by using the following equation: age × AST [IU/L]/platelet count [×100,000/L)] × sqrt(ALT [IU/L]), which is one the most commonly used scores for non-invasively estimating advanced liver fibrosis [17]. In particular, patients with MAFLD were considered to have indeterminate or advanced fibrosis if their FIB-4 index was ≥1.3 [17].

Statistical Analysis

Data are expressed as means±SD, medians and interquartile ranges (IQR), or percentages. Differences in clinical and biochemical characteristics, as well as in 24-hour Holter monitoring data in patients with T2DM, stratified by presence and severity of MAFLD, were assessed using the one-way analysis of variance for normally distributed variables and the Kruskal-Wallis test for non-normally distributed variables (such as diabetes duration, serum triglycerides, liver enzymes, as well as the number of APCs, and PVCs on 24-hour Holter monitoring). The chi-squared test was used to examine the between-group differences in categorical variables. Binary logistic regression models were used to assess the associations between MAFLD status and the risk of having either PSVT or ventricular tachyarrhythmias, which were included as the dependent variable. The following four forced-entry logistic regression models were performed: an unadjusted model; a model adjusted for age and sex (model 1); a model additionally adjusted for duration of diabetes, smoking, daily alcohol intake, HbA1c, triglycerides, obesity, hypertension (i.e., blood pressure ≥140/90 mmHg or use of any anti-hypertensive agents, including beta-blockers), CKD (or e-GFR values), COPD, ischemic heart disease (or valvular heart disease), and use of any anti-arrhythmic drugs (model 2); and, finally, a model further adjusted for echocardiographic LV ejection fraction (model 3). Covariates included

in these regression models were chosen as potential confounding factors based on their significance in univariable analyses or their biological plausibility. We also repeated the aforementioned logistic regression models, including the severity of MAFLD as covariate, instead of the presence/absence of MAFLD. In these regression models, the severity of MAFLD was assessed by ultrasonography and FIB-4 index and included as follows: no MAFLD *vs*. MAFLD and FIB-4 <1.3 *vs*. MAFLD and FIB-4 ≥1.3. A *p*-value of <0.05 was considered statistically significant. Statistical analyses were performed using STATA software, version 16.1 (STATA, College Station, TX, USA).

Results

Among the 367 outpatients with T2DM included in the study, 238 (64.9%) had MAFLD and 129 (35.1%) did not. Of the 238 patients with MAFLD, four patients had a history of excessive alcohol intake (>30 grams/day), and another one had a history of chronic hepatitis C; 110 (46.2%) of 238 patients with MAFLD had a FIB-4 index ≥1.3, which is indicative of indeterminate or advanced fibrosis; 46 of these 110 patients had a FIB-4 index ≥2.67, which is a cutoff highly indicative of advanced fibrosis. Of the whole sample, 173 (47.1%) patients had at least an episode of PSVT, 17 (4.6%) had paroxysmal AF and 102 (27.8%) had ventricular tachyarrhythmias (defined as non-sustained VT, >30 PVCs/h, or both) on 24-hour Holter monitoring data. No patients had sustained VT, abnormal serum TSH or electrolyte abnormalities.

The main clinical and biochemical characteristics of patients with T2DM, stratified by presence and severity of MAFLD are reported in **Table 1**. Compared to those without MAFLD, patients with MAFLD, irrespective of fibrosis status evaluated by FIB-4 index, were more likely to be younger, obese or active smokers, and had shorter duration of diabetes and higher prevalence of COPD. They also had higher levels of plasma total cholesterol, LDL-cholesterol, triglycerides, as well as higher values of e-GFR$_{CKD-EPI}$ than those without MAFLD. Sex, blood pressure, HbA1c, liver enzymes (except for serum AST level), electrolytes, LV ejection fraction (on echocardiography), as well as the prevalence of hypertension, ischemic heart disease, valvular heart disease, CKD and abnormal albuminuria did not significantly differ between the two patient groups. The use of glucose-lowering agents, statins, anti-hypertensive drugs (including beta-blockers) and anti-arrhythmic drugs were not significantly different between the two groups of patients. Finally, among the three patient

groups, patients with MAFLD and FIB-4 ≥1.3 had the lowest platelet count, the highest percentage of men and current smokers, as well as the highest values of serum AST and BMI.

The prevalence of supraventricular and ventricular tachyarrhythmias in patients stratified by MAFLD status is reported in **Figure 1A** and **Figure 1B**. Patients with T2DM and MAFLD had a significantly higher prevalence of paroxysmal AF (6.3% *vs*. 1.6%) and PSVT (51.7% *vs*. 38.8%), as well as a higher prevalence of PVCs >30 per hour (23.2% *vs*. 15.5%), non-sustained VT (15.1% *vs*. 3.1%), or both (31.9% *vs*. 20.2%) compared to their counterparts without MAFLD. Conversely, as reported in **Supplementary Table 1**, no significant differences were observed in terms of total heart rate, hourly APC count, APCs >30 per hour and hourly PCV count between the two patient groups.

The prevalence of supraventricular and ventricular tachyarrhythmias in patients stratified by severity of MAFLD is shown in **Figure 2A** and **Figure 2B**. In particular, the prevalence of PSVT progressively increased across the severity of MAFLD (being 54.5% among patients with MAFLD and FIB-4 index ≥1.3). Similarly, the prevalence of both non-sustained VT (20.8% among those with MAFLD and FIB-4 index ≥1.3) and ventricular tachyarrhythmias (36.6% among those with MAFLD and FIB-4 index ≥1.3) progressively increased across the severity of MAFLD.

The clinical and biochemical characteristics of T2DM patients, stratified by presence or absence of PSVT are reported in **Supplementary Table 2**. Compared with those without PSVT, patients with PSVT were more likely to be older, obese and had a higher prevalence of COPD, as well as higher values of HDL-cholesterol and (slightly) greater LV ejection fraction. In addition, they were also less frequently treated with metformin or diuretics. Notably, the presence and severity of MAFLD was significantly higher in patients with PSVT than in those without PSVT. All other clinical and biochemical variables (including serum electrolytes, use of beta-blockers or anti-arrhythmic agents, ischemic heart disease and valvular heart disease) did not significantly differ between the two patient groups.

The clinical and biochemical characteristics of T2DM patients, stratified by presence or absence of ventricular tachyarrhythmias are reported in **Supplementary Table 3**. Compared with those without ventricular tachyarrhythmias, patients with ventricular tachyarrhythmias were more likely to be male, and had higher values of total cholesterol, LV ejection fraction, as well as a higher prevalence

of CKD and COPD. They were also less treated with pioglitazone (although the total number of patients treated with this drug was very small) and tended to be more treated with sulphonylureas. Notably, the presence and severity of MAFLD was higher in those with ventricular tachyarrhythmias than in those without. All other clinical and biochemical variables (including serum electrolytes, hypertension, use of beta-blockers or anti-arrhythmic agents, ischemic heart disease and valvular heart disease) did not significantly differ between the two patient groups.

The association between the presence and severity of MAFLD and the risk of having PSVT is reported in **Table 2**. In unadjusted model, the presence of MAFLD was associated with ~70% increased risk of PSVT. This association remained significant after adjustment for age and sex (model 1), and even after further adjustment for smoking, alcohol intake, diabetes duration, HbA1c, triglycerides, obesity, hypertension, CKD, COPD, ischemic heart disease, and use of any anti-arrhythmic agents (model 2). Additional adjustment for LV ejection fraction did not attenuate the strength of this association (model 3). As also shown in the table, similar results were observed in multivariable regression models examining the association between the severity of MAFLD and the risk of PSVT. In model 2, patients with MAFLD and FIB-4 index ≥1.3 had an approximately twofold increased risk of PSVT compared to those without MAFLD. Further adjustment for LV ejection fraction slightly attenuated the strength of this association (model 3). Almost identical results were observed when we excluded from statistical analyses patients (n=33) treated with any anti-arrhythmic agents or those with a prior history of excessive alcohol intake (n=4) (data not shown). Due to the low number of cases with paroxysmal AF (n=17), the association between the presence of MAFLD and risk of paroxysmal AF was tested only in univariable regression analysis (unadjusted OR 4.27; 95% CI 1.01-18.9; *p*=0.047).

The association between the presence and severity of MAFLD and the risk of having ventricular tachyarrhythmias are reported in **Table 3**. In unadjusted model, the presence of MAFLD was associated with a nearly 90% increased risk of ventricular tachyarrhythmias. This association remained significant after adjustment for age and sex (model 1), and even in model 3 where additional adjustment was made for smoking, alcohol intake, diabetes duration, HbA1c, triglycerides, obesity, hypertension, CKD, COPD, ischemic heart disease, as well as use of any anti-arrhythmic agents and LV ejection fraction. As also shown in the table, almost identical results were observed in regression models where we examined the association between the severity of MAFLD

and the risk of ventricular tachyarrhythmias. In model 3, patients with MAFLD and FIB-4 index ≥1.3 had an approximately threefold increased risk of ventricular tachyarrhythmias compared to those without MAFLD. Again, similar results were observed when we excluded from statistical analyses patients who were treated with any anti-arrhythmic drugs or those with a prior history of excessive alcohol intake (n=4) (data not shown). In model 3, other variables that were independently associated with an increased risk of ventricular tachyarrhythmias (besides MAFLD) were male sex, older age and a lower LV ejection fraction on echocardiography.

Discussion

Our novel findings obtained in outpatients with T2DM show that the presence and severity of MAFLD (as detected by ultrasonography and FIB-4 index) was significantly associated with an increased risk of supraventricular tachyarrhythmias, including PSVT and paroxysmal AF. Moreover, the presence and severity of MAFLD was also significantly associated with an increased risk of ventricular tachyarrhythmias (defined as non-sustained VT, >30 PVCs per hour, or both); notably, all these associations remained statistically significant even after adjustment for common CVD risk factors, diabetes-related variables, medication use and other potential confounding factors.

To date, accumulating evidence indicates that NAFLD is associated with an increased risk of having or developing certain arrhythmias (especially permanent AF), irrespective of the presence of obesity, T2DM or other common CVD risk factors [18-24]. For instance, in a systematic review and meta-analysis of 9 cross-sectional and longitudinal studies (including ~365,000 individuals), we found that imaging-defined NAFLD was significantly associated with an increased risk of prevalent and incident AF, and that this association was stronger in people with T2DM [18]. In a cross-sectional study of 245 patients undergoing AF ablation, Decoin et al. reported that patients with MAFLD and increased liver fibrosis scores had adverse atrial remodeling (on echocardiography) and higher risk of AF recurrence following catheter ablation, compared to those without MAFLD [25]. Notably, to our knowledge, there are only a couple of published cross-sectional studies examining the association between MAFLD and risk of cardiac arrhythmias as assessed by 24-hour Holter monitoring. In a cross-sectional study of 330 Italian outpatients with T2DM referred for clinically indicated 24-hour Holter monitoring between 2013 and 2015, we showed for the first time that NAFLD on ultrasonography was associated with a higher risk of ventricular tachyarrhythmias (but

not supraventricular tachyarrhythmias), even after adjusting for coexisting CVD risk factors and potential confounders [19]. In such study, however, we did not have any data on severity of liver fibrosis. More recently, in a study including 358 Chinese patients with non-ST-segment elevation myocardial infarction, who received a 24-hour Holter monitoring after percutaneous coronary revascularization(s), Chen *et al.* reported that ultrasound-defined NAFLD was associated with a higher risk of >5 PVCs per hour, ventricular tachycardia or sinus arrest, even after adjusting for age, sex, obesity and other potential confounders [21]. Again, no data were available on the severity of liver fibrosis in such study. Collectively, therefore, our results corroborate and expand the findings of these two latter observational studies, supporting the existence of significant and independent associations between the presence and severity of MAFLD and risk of PSVT, paroxysmal AF or ventricular tachyarrhythmias in patients with T2DM undergoing a 24-hour Holter monitoring for clinical reasons. In this context, while it is known that paroxysmal AF is a CVD risk factor [26], recent studies have also reported that PSVT may be associated with a higher risk of ischemic/embolic strokes [27-29]. In addition, it should be noted that some forms of PSVT, such as atrio-ventricular nodal reentry tachycardia (AVNRT) or atrio-ventricular reentry tachycardia (AVRT), are also associated with higher risk of permanent AF [30], which is, in turn, associated with a higher risk of developing ischemic stroke, heart failure and death [31]. Finally, it is also known that ventricular tachyarrhythmias are associated with increased risk of CVD mortality [32].

Although the arrhythmogenic potential of MAFLD requires further confirmation in future studies, we believe that our results may have important clinical implications. Indeed, the increased risk of supraventricular and ventricular tachyarrhythmias observed among patients with T2DM and MAFLD, especially among those with higher liver fibrosis, might partly explain the increased risk of fatal and nonfatal CVD events seen in this patient population, thus further highlighting the clinical importance of CVD risk assessment in patients with MAFLD [33, 34]. Additionally, our results further emphasize the notion that MAFLD is a "multisystem" disease that requires a patient-centered, multidisciplinary and holistic approach to manage both liver disease and CVD risk [5].

To date, the putative biological mechanisms underpinning the association between MAFLD and risk of arrhythmias are not fully understood. The most obvious explanation for our findings is that the association between MAFLD and risk of supraventricular and ventricular tachyarrhythmias is simply an epiphenomenon of coexisting cardiometabolic risk factors, diabetes-related variables or

comorbidities. It is known that excessive alcohol intake is a risk factor for cardiac arrhythmias, especially for AF [35, 36], and that cigarette smoking, obesity, hypertension and other metabolic syndrome features are also important risk factors for cardiac arrhythmias [37, 38]. In addition, it should be noted that in our study, patients with PSVT were less frequently treated with metformin compared to those without PSVT, and that patients with ventricular tachyarrhythmias tended to be more frequently treated with sulphonylureas compared to those without ventricular tachyarrhythmias. Interestingly, different classes of glucose-lowering agents have shown distinct effects on the risk of cardiac arrhythmias (especially AF) in people with T2DM. In particular, it has been reported that sulphonylureas seem to be associated with a higher risk of cardiac arrhythmias and that metformin and other newer glucose-lowering agents (including SGLT-2 inhibitors and GLP-1 receptor agonists) may exert some favorable effects on risk of cardiac arrhythmias [39-43]. Moreover, some glucose-lowering agents (especially SGLT-2 inhibitors and GLP-1 receptor agonists) confer a meaningful cardiovascular protection in high-risk patients with T2DM [44, 45]. However, prospective controlled trials are required to confirm the positive effects of these glucose-lowering agents on cardiac arrhythmias in patients with T2DM. That said, our multivariable logistic regression analyses revealed that the significant association between MAFLD and risk of supraventricular/ventricular tachyarrhythmias persisted even after adjusting for common cardiometabolic risk factors, smoking history, alcohol intake, multiple comorbidities and other potential confounding factors, including medication use and LV ejection fraction. Hence, although future studies of well-characterized cohorts of MAFLD patients are needed, it is possible to hypothesize that MAFLD (especially MAFLD with increased levels of fibrosis) might contribute to the development of supraventricular and ventricular tachyarrhythmias, possibly through the exacerbation of systemic/hepatic insulin resistance and the systemic release of several hepatic mediators that may induce low-grade inflammation, pro-oxidative and pro-coagulant state and, ultimately, cardiac remodeling [6, 7, 46, 47]. For instance, a meta-analysis of 16 observational studies reported that NAFLD was associated with subclinical myocardial structural alterations (increased cardiac mass), as well as lower early diastolic relaxation (e') velocity, higher LV filling pressure, and larger left atrial volume [48]. It has been also reported that increased FIB-4 scores in NAFLD were associated with AF recurrence following ablation [49], and that the presence and severity of NAFLD on ultrasound was associated with prolonged heart rate-corrected QT (QTc) interval, which is an established risk factor for ventricular tachyarrhythmias and sudden cardiac death [50-52]. Finally, another possible mechanism involved in the association between MAFLD and

supraventricular and ventricular tachyarrhythmias might be cardiac autonomic dysfunction [6, 7]. Evidence suggests that NAFLD is associated with impaired cardiac sympathetic/parasympathetic balance, regardless of the presence or absence of T2DM and other CVD risk factors [53].

Our study has some important limitations that should be mentioned. First, this is a single-center, retrospective, cross-sectional study, which does not allow us to establish the temporality and causality of the observed associations. Second, a possible selection bias might have occurred, given that we included only outpatients with T2DM who underwent a first 24-hour Holter monitoring for clinical reasons. Hence, our findings may not necessarily be generalizable to other T2DM populations, especially those with a more favorable CVD risk profile. However, we chose to study this specific group of T2DM outpatients (who are at high risk of having cardiac arrhythmias), because we believe that this choice might increase our chance of finding differences, if any, between patients with and without MAFLD by using a reasonably large sample size (such as the one in this study). Third, although our logistic regression models were extensive, we cannot exclude the possibility of residual confounding by some unmeasured factors that might, at least in part, explain the observed associations. Finally, the identification of MAFLD and fibrosis severity was based on ultrasonography and FIB-4 index (which is one of the most widely used non-invasive biomarkers of advanced fibrosis [17]), but was not confirmed either by liver biopsy (which is the "gold standard" for staging fibrosis) or by magnetic resonance-proton density fat fraction, vibration-controlled transient elastography or magnetic resonance elastography [14]. Moreover, the number of MAFLD patients with a FIB-4 index ≥2.67 (i.e., a cutoff that is highly indicative of advanced fibrosis) was relatively low (n=46, 12.5% of total) and did not allow us to perform logistic regression models with extensive adjustment for possible confounders.

Notwithstanding these limitations, we believe that our study has important strengths, such as the relatively large sample size, the completeness of the dataset, the ability to adjust for important cardiovascular risk factors and potential confounding factors, and the exclusion of patients with implantable cardioverter defibrillators or pacemakers, as well as those with a history of alcohol abuse, permanent AF, kidney failure, or cirrhosis. We believe that inclusion of patients with such complications might have confounded the interpretation of data.

In conclusion, the results of our cross-sectional study show that patients with T2DM and MAFLD have an increased risk of prevalent PSVT and ventricular tachyarrhythmias compared to their counterparts without MAFLD. The magnitude of this risk increases with the severity of liver disease in MAFLD (especially with higher levels of FIB-4 index). Furthermore, this risk remains statistically significant even after adjustment for common CVD risk factors, diabetes-related variables, comorbidities, use of medications and echocardiographic LV ejection fraction. Future studies are needed to further validate these results in larger cohorts of patients and to better elucidate the putative biological mechanisms underpinning the observed associations between the presence and severity of MAFLD and the risk of having or developing supraventricular and ventricular tachyarrhythmias.

Table 1. Clinical and biochemical characteristics of patients with type 2 diabetes, stratified by presence and severity of MAFLD.

	Patients without MAFLD (n=129)	Patients with MAFLD and FIB-4 <1.3 (n=137)	Patients with MAFLD and FIB-4 ≥1.3 (n=101)	*P* values
Age (years)	73±9	69±9	73±8	0.001
Male sex (%)	52.7	57.7	69.3	0.036
BMI (kg/m^2)	26.5±4.7	30.6±5.4	31.2±7.9	0.001
Obesity (%)	29.5	55.5	50.5	0.001
Diabetes duration (years)	13 (7-25)	8 (3-16)	10 (4-20)	0.002
Current smokers (%)	2.3	12.4	13.9	0.005
Systolic blood pressure (mmHg)	132±18	135±17	137±18	0.105
Diastolic blood pressure (mmHg)	76±10	76±10	77±10	0.691
Platelet count (x 100,000/mm^3)	244±84	254±60	198±54	0.001
Glucose (mg/dL)	140±45	135±43	137±41	0.663
Hemoglobin A1c (%)	7.4±1.4	7.3±1.6	7.3±1.6	0.684
Total cholesterol (mg/dL)	143±36	157±43	146±36	0.010
LDL-cholesterol (mg/dL)	69±28	80±36	73±30	0.039
HDL-cholesterol (mg/dL)	50±16	47±14	48±13	0.251
Triglycerides (mg/dL)	113 (77-139)	128 (94-175)	124 (88-164)	0.005
AST (IU/L)	20 (16-25)	17 14-21)	25 (20-31)	0.001
ALT (IU/L)	22 (16-31)	22 (17-29)	23 (16-35)	0.577
GGT (IU/L)	26 (16-44)	25 (17-44)	32 (16-68)	0.126
Creatinine (mg/dL)	1.2±0.6	1.0±0.4	1.2±0.6	0.039
e-GFR$_{CKD-EPI}$ (mL/min/1.73 m^2)	63±24	71±22	65±24	0.011
Sodium (mmol/L)	140±3	140±3	140±3	0.827
Potassium (mmol/L)	4.2±0.5	4.1±0.4	4.2±0.5	0.548
Hypertension (%)	84.5	89.8	92.0	0.177
Ischemic heart disease (%)	35.9	35.8	41.6	0.598
Valvular heart disease (%)	15.6	10.8	15.0	0.475
Abnormal albuminuria (%)	29.5	24.1	37.6	0.075
CKD (%)	52.7	45.3	59.4	0.063
COPD (%)	3.1	10.9	8.9	0.050
Insulin therapy (%)	36.4	31.1	36.0	0.607
Metformin (%)	53.5	62.0	50.5	0.165
Sulphonylureas (%)	25.6	17.6	30.7	0.055
Pioglitazone (%)	2.3	2.9	3.0	0.942
DPP-4 inhibitors (%)	21.7	11.7	14.9	0.078
GLP-1 receptor agonists (%)	9.3	7.3	7.9	0.832
SGLT-2 inhibitors (%)	4.7	7.3	4.9	0.601
Antiplatelet drugs (%)	53.5	63.5	68.3	0.060
Beta-blockers (%)	48.1	50.4	50.5	0.911
ARB/ACE-inhibitors (%)	70.5	67.9	77.2	0.279
Calcium-channel blockers (%)	19.6	22.6	26.7	0.338
Diuretics (%)	51.2	58.4	53.5	0.482
Statins (%)	72.3	70.8	74.3	0.698
Antiarrhythmic agents (%)	9.3	8.0	9.9	0.873
LV ejection fraction (%) on echocardiography (n=244)	52±13	54±11	55±11	0.286

Sample size, *n*=367, except where indicated. Data are expressed as means ± SD, medians and IQR (in parenthesis) or relative percentages. Differences between the three groups were tested by using the one-way analysis-of-variance (ANOVA) for normally distributed variables, the Kruskal-Wallis test for non-normally distributed variables (such as diabetes duration, serum triglycerides and liver enzymes) and the chi-squared test. Obesity was defined as BMI ≥30 kg/m^2. CKD was defined as e-GFR <60 mL/min/1.73 m^2. Hypertension was defined as blood pressure ≥140/90 mmHg or drug treatment. for categorical variables.

Abbreviations: ACE: angiotensin-converting enzyme; ALT: alanine aminotransferase; ARB: angiotensin II receptor blocker; AST: aspartate aminotransferase; BMI: body mass index; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DPP-4: dipeptidyl peptidase-4; e-GFR: estimated glomerular filtration rate; GGT: gamma-glutamyltransferase; GLP-1: glucagon-like peptide-1; LV: left ventricular; MAFLD: metabolic dysfunction-associated fatty liver disease; SGLT-2: sodium/glucose cotransporter-2.

Table 2. Association between the presence and severity of MAFLD and the risk of paroxysmal supraventricular tachycardia in patients with type 2 diabetes.

Logistic Regression Models	Odds ratio(s)	95% CIs	*P* values
Presence of MAFLD			
Unadjusted model			
MAFLD (yes vs. no)	1.68	1.09 – 2.61	0.018
Adjusted model 1			
MAFLD (yes vs. no)	1.86	1.18 – 2.91	0.007
Adjusted model 2			
MAFLD (yes vs. no)	2.06	1.22 – 3.46	0.007
Adjusted model 3			
MAFLD (yes vs. no)	2.04	1.04 – 4.00	0.037
Severity of MAFLD			
Unadjusted model			
No MAFLD (n=129)	*Ref.*	*Ref.*	-
MAFLD and FIB-4 <1.3 (n=137)	1.56	0.96 – 2.53	0.070
MAFLD and FIB-4 ≥1.3 (n=101)	1.89	1.11 – 3.20	0.018
Adjusted model 1			
No MAFLD (n=129)	*Ref.*	*Ref.*	-
MAFLD and FIB-4 <1.3 (n=137)	1.86	1.12 – 3.10	0.017
MAFLD and FIB-4 ≥1.3 (n=101)	1.85	1.08 – 3.17	0.026
Adjusted model 2			
No MAFLD (n=129)	*Ref.*	*Ref.*	-
MAFLD and FIB-4 <1.3 (n=137)	1.96	1.10 – 3.49	0.022
MAFLD and FIB-4 ≥1.3 (n=101)	2.18	1.19 – 3.97	0.011
Adjusted model 3			
No MAFLD (n=97)	*Ref.*	*Ref.*	-
MAFLD and FIB-4 <1.3 (n=81)	2.12	0.99 – 4.57	0.052
MAFLD and FIB-4 ≥1.3 (n=66)	1.96	0.96 – 4.23	0.063

Sample size, *n*=367, except for adjusted model 3 where adjusted model 3 where only patients with echocardiographic data were included (n=244). Data are expressed as odds ratios ± 95% confidence intervals (CIs) as assessed by either univariable (unadjusted) or multivariable logistic regression analyses. The presence of PSVT (defined as at least an episode of PSVT during 24-hour Holter-monitoring) was included as the dependent variable.

Other covariates included in the three progressive multivariable regression models, along with NAFLD, were as follows: model 1: adjusted for age and sex; <u>model 2</u>: further adjusted for smoking history, **daily alcohol intake**, diabetes duration, HbA1c, triglycerides, obesity, hypertension (i.e., blood pressure ≥140/90 mmHg and/or use of any anti-hypertensive agents, *including* beta-blockers), CKD, COPD, ischemic heart disease, and use of any antiarrhythmic drugs; <u>model 3</u>: adjustment for the same covariates included in model 2 *plus* LV ejection fraction on echocardiography.

Table 3. Association between presence and severity of MAFLD and the risk of ventricular tachyarrhythmias in patients with type 2 diabetes.

Logistic Regression Models	Odds ratio(s)	95% CIs	*P* values
Presence of MAFLD			
Unadjusted model			
MAFLD (yes vs. no)	1.86	1.12 – 3.09	0.017
Adjusted model 1			
MAFLD (yes vs no)	1.83	1.08 – 3.10	0.025
Adjusted model 2			
MAFLD (yes vs. no)	1.72	0.98 – 3.14	0.061
Adjusted model 3			
MAFLD (yes vs. no)	2.44	1.16 – 5.11	0.018
Severity of MAFLD			
Unadjusted model			
No MAFLD (n=129)	*Ref.*	*Ref.*	-
MAFLD and FIB-4 <1.3 (n=137)	1.58	0.89 – 2.78	0.116
MAFLD and FIB-4 ≥1.3 (n=101)	2.29	1.27 – 4.13	0.006
Adjusted model 1			
No MAFLD (n=129)	*Ref.*	*Ref.*	-
MAFLD and FIB-4 <1.3 (n=137)	1.70	0.94 – 3.09	0.810
MAFLD and FIB-4 ≥1.3 (n=101)	1.99	1.08 – 3.65	0.027
Adjusted model 2			
No MAFLD (n=129)	*Ref.*	*Ref.*	-
MAFLD and FIB-4 <1.3 (n=137)	1.54	0.80 – 3.06	0.186
MAFLD and FIB-4 ≥1.3 (n=101)	1.93	1.01 – 3.77	0.049
Adjusted model 3			
No MAFLD (n=97)	*Ref.*	*Ref.*	-
MAFLD and FIB-4 <1.3 (n=81)	1.99	0.93 – 4.58	0.080
MAFLD and FIB-4 ≥1.3 (n=66)	2.97	1.30 – 6.77	0.010

Sample size, *n*=367, except for adjusted model 3 where only patients with echocardiographic data were included (n=244). Data are expressed as odds ratios ± 95% confidence intervals (CIs) as assessed by either univariable (unadjusted) or multivariable logistic regression analyses. The presence of ventricular tachyarrhythmias (defined as presence of non-sustained VT, >30 PVCs per hour, or both) was included as the dependent variable.

Other covariates included in the three progressive multivariable regression models, along with NAFLD, were as follows: *model 1*: adjusted for age and sex; *model 2*: further adjusted for smoking history, **daily alcohol intake,** diabetes duration, HbA1c, triglycerides, obesity, hypertension (*i.e.,* blood pressure ≥140/90 mmHg and/or use of any anti-hypertensive agents, *including* beta-blockers), CKD, COPD, ischemic heart disease, and use of any antiarrhythmic drugs; *model 3*: adjustment for the same covariates included in model 2 *plus* LV ejection fraction on echocardiography.

Figure Legends

Figure 1. Prevalence of supraventricular (A) or ventricular tachyarrhythmias (B) on 24-hour Holter monitoring among patients with T2DM, stratified by presence of MAFLD.

Figure 2. Prevalence of supraventricular (A) or ventricular tachyarrhythmias (B) on 24-hour Holter monitoring among patients with T2DM, stratified by severity of MAFLD.

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