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Reply to Dr. Chiang's comments

We would like to thank Dr. Chiang for his scientific interest [1] in our recent cross-sectional study assessing the association between the presence and severity of MAFLD (assessed by ultrasonography and Fibrosis-4 index [FIB-4], i.e., one of the most commonly used non-invasive blood-based biomarkers for assessing advanced fibrosis) and the risk of supraventricular and ventricular tachyarrhythmias in patients with type 2 diabetes mellitus (T2DM), who underwent a 24-hour Holter monitoring for clinical indications [2].

Our responses to the comments raised by Dr. Chiang [1] are as follows:

1. The prevalence of moderate or severe valvular heart diseases (defined as described in the medical records, including diagnostic symptoms and echocardiogram results) was not significantly different when the study participants were stratified by the presence and severity of MAFLD. As reported in Table 1, the prevalence of valvular heart disease was 15.6% in patients without MAFLD, 10.8% in those with MAFLD and FIB-4 <1.3 and 15.0% in those with MAFLD and FIB-4 >1.3 (p=0.475). In addition, the prevalence of valvular heart disease did not significantly differ when the study participants were stratified either by presence or absence of paroxysmal supraventricular tachycardia (Table S2), or by presence or absence of ventricular tachyarrhythmias (Table S3). That said, we have now also repeated the fully adjusted logistic regression models (presented in Tables 2 and 3) and added as an additional covariate the presence of valvular heart disease. Notably, the results remained almost identical confirming that the presence and severity of MAFLD was independently associated with an increased risk of having supraventricular and ventricular tachyarrhythmias.
2. Liver biopsy assessment is an invasive diagnostic method that has some important limitations (mainly related to risk, cost and resource utilization), and liver biopsy is difficult to perform in large epidemiological studies. Moreover, liver biopsy is difficult to justify in subjects with fairly normal serum aminotransferase concentrations (such as those observed in the vast majority of our study participants).
3. As reported in the Results section of our article, among the study participants there were four T2DM patients who had a history of excessive alcohol intake (defined as > 30 g/day), and another one who had a prior history of chronic hepatitis C. We decided to not exclude these five individuals from statistical analyses because the newly proposed definition of MAFLD does not have as a pre-requisite the exclusion of other secondary causes of steatotic liver disease. In addition, we would underline that the four individuals with a history of excessive alcohol intake drank between 50-60 grams of alcohol per day, and none of these subjects (including also the subject with a prior history of chronic hepatitis C) had any clinical, biochemical or ultrasonographic data suggestive of cirrhosis. That said,

as already reported in our manuscript, the main results of our study remained essentially unchanged when we excluded from statistical analyses the four patients who had a prior history of excessive alcohol intake.

4. We agree with the comment(s) raised by Dr. Chiang on the inherent limitations of a retrospective, cross-sectional study like this one. Indeed, in the paragraph stating the possible limitations of our study, we had recognized that this is a single-center, retrospective, cross-sectional study, which does not allow us to establish the temporality and causality of the observed associations. In addition, we had also recognized that 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 patient groups with T2DM, especially those with a more favorable cardiovascular risk profile.

References

1. Chiang O. Letter to the Editor. Diabetes Metab 2023; in press.
2. Mantovani A, Csermely A, Taverna A, Cappelli D, Benfari G, Bonapace S, et al. Association between metabolic dysfunction-associated fatty liver disease and supraventricular and ventricular tachyarrhythmias in patients with type 2 diabetes. Diabetes Metab 2023;49:101416.