Liver Stiffness, Not Fat Liver Content, Predicts the Length of QTc Interval in Patients with Chronic Liver Disease

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Abstract

The severity of fatty liver at ultrasound has been associated with QT length, a finding invoked to explain the excess cardiovascular risk of patients with fatty liver. However, the ability of ultrasound to stage accurately the severity of fatty liver is limited, with fibrosis a major confounder. Here, we aimed to verify the alleged relationship between fat liver content and QT length using a technique apt at discriminating steatosis from fibrosis noninvasively, i.e., transient elastography (TE) with measure of liver stiffness (LS) and controlled attenuation parameter (CAP). A prospectively collected derivation cohort of 349 patients with chronic liver disease (CLD) of any etiology (N = 105 with nonalcoholic fatty liver) was studied to identify clinical, laboratory, and instrumental predictors of the corrected QT interval (QTc) and QTc prolongation, including LS and CAP. The results were validated on a subgroup of patients belonging to the derivation cohort (out of sample validation), as well as on a completely different group of N = 149 subjects with CLD (out of time validation). QTc values were directly related to liver stiffness (LS; ρ = 0.137; p = 0.011), heart rate (HR; ρ = 0.307; p < 0.001), and age (ρ = 0.265; p < 0.001) and were significantly longer in females (p < 0.001). In contrast, QTc was not associated with the value of controlled attenuation parameter (ρ = 0.019; p = 0.718); moreover, no discernible differences in QTc length were noted based on CLD etiology. QTc was prolonged in 24/349 patients (6.9%); age, HR, and LS were independent predictors of QTc prolongation (χ² = 23.7, p < 0.001). Furthermore, QTc values (after logarithmic transformation) were predicted by a model including age, gender, HR, and LS (F = 14.1, R² = 0.198, p < 0.001). These latter results were validated by both out-of-sample and out-of-time methods. In conclusion, TE findings strongly suggest that among patients with CLD, fibrosis, not steatosis, is a major determinant of QTc length.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is an important health concern, being on a global scale the most prevalent chronic liver disease (CLD). Its severity ranges from simple steatosis, to nonalcoholic steatohepatitis (NASH) with or without fibrosis, to cirrhosis [1]. Most of NAFLD patients, however, do not die because of the liver disease itself but of heart disease [2]. Indeed, NAFLD has been associated to an increased risk of fatal and nonfatal cardiovascular diseases [3] and is an independent predictor of atrial fibrillation [4]. Interestingly, the presence and severity of findings consistent with a fatty liver on ultrasound are associated with a prolonged corrected QT (QTc) interval both among patients with type 2 diabetes mellitus [5] and in the general population. Since QT length predicts cardiovascular death even when it is within limits considered normal, it is tempting to attribute to its prolongation part of the excess cardiovascular mortality of NAFLD patients. The mechanisms underlying the association between QT length and fatty liver are unclear, though they seem to be independent of traditional cardiometabolic factors and of systemic inflammation [6].

The development of CLD is often complicated by alterations in other organs and systems, including the heart. The
so-called cirrhotic cardiomyopathy, defined as a chronic cardiac dysfunction observed in patients with cirrhosis, is characterized by blunted contractile responsiveness to stress, and/or altered diastolic relaxation with electrophysiological abnormalities, in the absence of any other known cause of cardiac disease [7]. One of the major electrophysiological abnormalities of cirrhotic cardiomyopathy is QTc prolongation [8]. It is important to note that, in the presence of fibrosis, the specificity of ultrasound in identifying fatty liver is substantially diminished [9]; therefore, the alleged association between length of the QT interval and NAFLD would be better explored by simultaneously quantifying fibrosis and steatosis, which is not feasible with conventional ultrasound. Demonstrating that NAFLD patients have significantly longer QTc intervals when compared to patients with CLD of different etiologies would give further support to the true existence of this association.

Based on these premises, in the present paper, we aimed to investigate the relative strength of the association of fibrosis and steatosis with QTc prolongation, both in NAFLD and in chronic liver diseases of different etiologies with or without evidence of fatty liver. To fulfill these aims, in a cohort of CLD patients, we quantified noninvasive steatosis and fibrosis at the same time the QTc interval was measured. Using these data, we developed and validated a model to predict the length of the QTc interval in such patients.

2. Materials and Methods

Our research was conducted according to the principles of the Declaration of Helsinki. All the procedures were performed in clinical practice and, therefore, a specific approval from the Ethical Committee was not required. However, every patient signed an informed consent for the anonymous distribution of data for research proposal. Firstly, a cross-sectional derivation cohort was identified among consecutive patients attending the liver clinic of a university hospital. We included adult patients (older than 18 years), who received a diagnosis of chronic liver diseases from any etiology. We excluded patients affected by atrial fibrillation, atrial flutter, atrioventricular block, and right or left bundle block; those who had experienced a myocardial infarction; those who had undergone pacemaker implantation; and those who were receiving drugs known to prolong the QTc interval or antiarrhythmic drugs. Patients receiving “conditional risk” drugs were allowed; “conditional risk” drugs are potentially responsible of QTc prolongation but only under specific circumstances (i.e., drug overdose, drug interaction, or in case of long QT syndrome).

After the application of the inclusion and exclusion criteria, we identified 349 patients; 105 were affected by NAFLD, 200 by chronic viral hepatitis, 12 by alcoholic liver disease, 3 by inherited diseases, 14 by autoimmune hepatitis and, finally, 16 by cryptogenic liver diseases.

A validation cohort of 149 patients was further selected, according to similar inclusion and exclusion criteria; out of them, 50 were affected by NAFLD, while 99 were affected by chronic viral hepatitis.

The demographic and clinical data collected included age, gender, smoking and alcohol habits, past medical history, and concomitant treatment(s). Moreover, all patients underwent a thorough physical examination. The body mass index (BMI) was calculated as body weight in kg (measured with the patient wearing light underwear) divided by the square of the height in meters and interpreted according to the World Health Organization classification [10]. The waist circumference (WC) was measured midway between the lowest rib and the iliac crest when standing. Blood pressure was measured after a period of relaxation in the seated position using a manual sphygmomanometer.

All the patients underwent a transient elastography examination by FibroScan® (Echosens, Paris, France), after at least 6 hours of fasting. This exam was performed by a single expert hepatologist, blinded to the results of ECG, as previously reported [11]. The rate of successful measurements was calculated as the ratio of validated measurements to total measurements. The examination was considered reliable if at least 10 validated measurements were obtained for the patient with a greater than 65% success rate and if the interquartile range of all validated measurements was lower than 30% of the median value. The median value of successful measurements was considered to be representative of liver stiffness (LS) and was expressed in kilopascals. Liver fibrosis was ruled out in case of LS < 6 kPa. Moreover, all patients included in the derivation cohort also underwent a measurement of the controlled attenuation parameter (CAP), which allows noninvasive semiquantitative assessment of liver fat content by measuring the attenuation at the center frequency of the FibroScan® probe, ensuring that the liver ultrasonic attenuation was obtained simultaneously from the same volume of liver parenchyma as the LS. CAP values range from 100 to 400 dB/m: the cutoff values we chose to indicate steatosis as absent, mild, moderate, and severe were <215 dB/m, ≥215 dB/m, ≥252 dB/m, and ≥296 dB/m, respectively [12]. A 12-lead ECG trace (length: 10 seconds) was recorded by a trained nurse with the participant in the supine position on the morning of the same day of the visit. The QTc value was obtained recording the electrocardiogram by an interpretive machine (600G, Contec, No.112 Qinhuang West Street, Economic &Technical Development Zone, Qinhuangdao, Hebei Province, 66000, China) and was considered normal when <450 msec in males and <470 msec in females [13]. Resting heart rates were obtained from ECG readings.

3. Statistical Analysis

Anthropometric, clinical, and biochemical data were recorded in a database and analyzed by the statistical software package Stata, version 15.1 (StataCorp LP, College Station, Texas, US). The measures of centrality and dispersion of data chosen were medians and 95% CI. Medians were compared between groups by the Mann–Whitney and Kruskal–Wallis (K–W) tests. Exact Fisher’s test and Pearson’s χ² test were used, as appropriate, to explore the associations of categorical variables. Cuzick’s test was used
to test the trend of a continuous variable between groups [14]. The association between continuous variables was tested by Spearman’s correlation. Models were built to predict a set of explanatory variables: (a) a significantly prolonged QTc (by logistic regression analysis) and (b) the actual QTc value (multiple linear regression analysis; due to nonnormal distribution, the dependent variable had to be transformed logarithmically). Then, we performed an out-of-sample validation of the regression model, by evaluating whether the results obtained were similar when the model was applied to two subsamples of $N = 175$ and $N = 174$ patients randomly selected from the derivation cohort (samples A and B, respectively). The concordance between predicted and measured QTc was verified in a Bland-Altman plot.

Furthermore, we performed an out-of-time validation, by applying the model obtained from the derivation cohort to the validation cohort. The concordance between measured and expected QTc was also tested by Bland-Altman analysis. We calculated Lin’s concordance coefficient between measured and expected QTc for both the validation methods.

The level of significance chosen for all statistical analysis was 0.05 (two-tailed).

## 4. Results

### 4.1. Derivation Cohort

The derivation cohort included 349 patients, whose main features are listed in Table 1.

Table 1: Main demographic and clinical features of the derivation cohort. Continuous variables are shown as medians (IQR), while categorical variables are shown as frequencies (%).

| Gender, $N$       |          |
|-------------------|----------|
| Males             | 193 (55.3%) |
| Females           | 156 (44.7%) |

| Age, years        | 63 (52 – 72) |
| Liver stiffness, kPa | 6.0 (4.8 – 7.7) |
| CAP, dB/m         | 242 (213 – 285) |
| Etiology of liver disease |
| NAFLD             | 105 (30.1%)  |
| Chronic viral hepatitis | 200 (57.3%)  |
| Other etiologies   | 44 (12.6%)   |
| BMI, kg/m$^2$      | 25.7 (23.5 – 29.3) |
| <25                | 154 (44.1%)  |
| 25-29.9            | 124 (35.5%)  |
| ≥30                | 71 (20.4%)   |
| Waist circumference, cm |
| Males             | 98 (90 – 107) |
| Females           | 102 (94 – 109) |
| T2DM, $N$         |
| No                | 279 (79.9%)  |
| Yes               | 70 (20.1%)   |
| Alcohol consumption, $N$ |
| No                | 202 (57.9%)  |
| Regular consumption | 119 (34.1%)  |
| Regular alcohol abuse | 27 (7.7%)   |
| Binge drinking    | 1 (0.3%)     |
| Cigarettes smoke, $N$ |
| Never smoked      | 146 (41.8%)  |
| Previous smoker   | 138 (39.5%)  |
| Current smoker, <15 cigarettes daily | 39 (11.2%) |
| Current smoker, ≥15 cigarettes daily | 26 (7.5%) |
| Physical activity, $N$ |
| Sedentary lifestyle | 149 (42.7%) |
| <30 minutes of walk/day | 96 (27.5%) |
| ≥30 minutes of walk/day | 104 (29.8%) |

Abbreviations: BMI: body max index; CAP: controlled attenuation parameter; NAFLD: nonalcoholic fatty liver disease; QTc: corrected QT interval; T2DM: type 2 diabetes mellitus.

In a multivariable logistic regression analysis, age, heart rate, and LS were confirmed as independent predictors of QTc prolongation ($\chi^2 = 23.7, p < 0.001$; Table 4(a)); we also

QTc was prolonged in 24/349 patients (6.9%); out of them, 18 (75%) were affected by viral hepatitis, 5 (21%) by NAFLD, and 1 (7%) by alcoholic liver disease. In Table S3, we report the main features of the subjects showing a prolonged QTc. Among these, there was a significantly higher proportion of cirrhotic patients (25.0% vs. 7.1%, $p = 0.009$), but a similar proportion of patients with severe steatosis (33.3% vs. 21.0%; $p = 0.12$).

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4.2. Out-of-Sample Validation. To confirm the results obtained from the derivation cohort, we randomly selected 175 patients from the same cohort (sample A) and we evaluated whether the results of the multiple linear regression might be replicated in this subgroup of subjects. As shown in Table 5, the results were similar ($F = 10.2$, $R^2 = 0.268$, $p < 0.001$).

We used the equation obtained from the analysis reported in Table 4 to calculate the log-transformed QTc values in the remaining 174 patients (sample B) of the derivation cohort. The predicted QTc was significantly associated to the measured QTc in the sample B patients ($p = 0.417$; $p < 0.001$; Figure 1(a)), as confirmed by Bland-Altman analysis (Figure 1(b)).

**Table 2**: QTc values in different categories of patients. The table shows the differences of QTc values in different categories of patients according to some relevant categorical and continuous variables. The median value of QTc is shown as median (IQR).

| Variable     | QTc (msec) | $p$   |
|--------------|------------|-------|
| Gender       |            |       |
| Males (N = 193) | 402 (387 - 420) |       |
| Females (N = 156) | 411 (397 - 438) | $<0.001$ |
| BMI, kg/m$^2$ |            |       |
| $\leq 24.9$ (N = 154) | 409 (392 - 425) |       |
| $25.0 - 29.9$ (N = 124) | 407 (387 - 428) |       |
| $\geq 30.0$ (N = 71) | 406 (391 - 428) | 0.609 |
| T2DM         |            |       |
| No (N = 279)  | 407 (390 - 426) |       |
| Yes (N = 70)  | 410 (396 - 430) | 0.269 |
| LS, kPa      |            |       |
| $< 5.9$ (N = 163) | 406 (388 - 426) |       |
| $5.9 - 12.9$ (N = 157) | 406 (391 - 425) |       |
| $\geq 13$ (N = 29) | 425 (409 - 461) | 0.013 |
| CAP (dB/m)   |            |       |
| $< 215$ (N = 94) | 408 (393 - 423) |       |
| $215 - 296$ (N = 182) | 406 (391 - 428) |       |
| $\geq 296$ (N = 62) | 408 (390 - 433) | 0.434 |

**Table 3**: Differences according to CLD diagnosis. The table shows the differences according to the underlying cause of chronic liver disease. The continuous variables are shown as medians (IQR), while categorical variables are shown as N (%).

| Variable     | NAFLD     | Other etiologies | $p$   |
|--------------|-----------|-----------------|-------|
| LS, kPa      | 5.6 (4.5-6.7) | 6.2 (5.0-8.0) | 0.0004 |
| CAP, dB/m    | 288 (259-334) | 230 (203-263) | <0.0001 |
| QTc, msec    | 408 (392-429) | 407 (391-425) | 0.60  |
| CR drugs, N (%) | 30 (28.6) | 50 (20.5) | 0.12  |

**Table 4**: Predictors of QTc value. In (a), we show the results of the multivariable logistic regression analysis testing for potential predictors of QTc prolongation; in (b), the results of a multiple regression analysis built to predict the QTc value in the derivation cohort (after logarithmic transformation) are shown.

(a) | Variable | Odds ratio (95% CI) | $p$ |
|------|-----------|-------------------|-----|
| Age  | 1.044 (1.004 - 1.086) | 0.031 |
| Gender* | 0.828 (0.333 - 2.061) | 0.685 |
| HR   | 1.060 (1.017 - 1.104) | 0.005 |
| CR drugs* | 0.845 (0.299 - 2.386) | 0.751 |
| LS   | 1.078 (1.022 - 1.136) | 0.006 |
| CAP  | 1.005 (0.997 - 1.012) | 0.236 |

(b) | Variable | Coefficient (95% CI) | $p$ |
|------|-----------|---------------------|-----|
| Age  | 0.001 (0.000 - 0.002) | <0.001 |
| Gender* | -0.023 (-0.040 - 0.007) | 0.004 |
| HR   | 0.002 (0.001 - 0.003) | <0.001 |
| CR drugs* | 0.010 (-0.008 - 0.003) | 0.250 |
| LS   | 0.003 (0.001 - 0.004) | 0.001 |
| CAP  | 0.000 (0.000 - 0.000) | 0.433 |
| Constant | 5.786 (5.718 - 5.855) | <0.001 |

**Table 5**: Multiple regression analysis in the sample A. Herein, we show the results of the multiple linear regression of the QTc value (after logarithmic transformation) in a subgroup of 175 patients randomly selected from the derivation cohort.

| Variable | Coefficient (95% CI) | $p$ |
|------|---------------------|-----|
| Age  | 0.001 (0.000 - 0.002) | 0.002 |
| Gender* | -0.037 (-0.060 - 0.015) | <0.001 |
| HR   | 0.002 (0.001 - 0.003) | <0.001 |
| CR drugs* | 0.009 (-0.002 - 0.004) | 0.578 |
| LS   | 0.003 (0.000 - 0.005) | 0.020 |
| CAP  | 0.000 (0.000 - 0.000) | 0.761 |
| Constant | 5.786 (5.695 - 5.877) | <0.001 |
4.3. Out-of-Time Validation. To further validate our model, we applied the equation derived from the derivation cohort to a validation cohort. The validation cohort was composed by 149 patients (95 males, 63.8%), median age 60 (50-74) years. Fifty patients (33.6%) had NAFLD and 99 (66.4%) chronic viral hepatitis. The median BMI was 26.2 (23.6-29.9) kg/m².

As shown in Figure 2(a), the measured QTc and the predicted QTc were significantly associated ($\rho = 0.533$; $p < 0.001$), as further confirmed by Bland-Altman plot (Figure 2(b)).

5. Discussion

QTc prolongation has been reported both in patients with cirrhosis and in those with nonalcoholic fatty liver disease. In the present study, we provide data suggesting that liver fibrosis is a stronger determinant of QTc prolongation than fatty liver, independent of the etiology of chronic liver disease. These findings need to be discussed at the light of the existing literature on this topic and of the limitations of the noninvasive techniques employed to determine the presence/absence of fatty liver and fibrosis.
Among similar classes of liver stiffness, we found similar QTc values independent of the severity of liver steatosis and the etiology of liver disease suggesting that, among patients with liver disease, QTc prolongation is not confined to a specific etiology. This is in line with previous reports from other groups [8, 15]. The fact that QTc is not different between conditions known to have a different prevalence of steatosis indirectly suggests that fatty liver might not be relevant in QTc prolongation [16]. At variance with the findings observed by others with an ultrasound methodology [5], CAP-assessed fat liver content bore no relationship to the length of the QTc interval. There could be several explanations for this discrepancy, including the different ethnic backgrounds of the populations studied and/or the subtlety of the association, which may require a very large sample size to be detected. It is important to note, however, that the estimate of liver fat content obtained by measuring the CAP is more objective than that obtainable by ultrasound. Besides, the mechanism underlying this postulated association is unknown yet. It has been proposed that QTc prolongation could be the result of an overactivation of sympathetic system [17]; since this issue was not specifically investigated in our paper, we cannot confirm or refute this hypothesis. However, it has long been known that sympathetic activation is common in compensated cirrhosis [18]. Here, we show that a proxy measure of liver fibrosis, LS measured by transient elastography is independently related to QTc length. Even if LS was previously shown to correlate not only with liver fibrosis but also with other histological figures like necroinflammatory activity, it reflects liver damage: the more severe liver damage is, the higher LS is. It must be said that the association between LS and QTc is rather weak, when considering the entire study population; however, it is influenced by CLD etiology, becoming stronger when NAFLD patients are excluded from the analysis (data not shown). Indeed, the association between LS and QTc was not observed in NAFLD patients, a fact that may be due to their (likely) lower necroinflammatory activity, their lower prevalence of cirrhosis, and/or the known difficulty in diagnosing cirrhosis by TE in this disease [19]. In the present study, QTc was found significantly longer in patients with liver stiffness equal or higher than 13 kPa, which many would consider a reliable cutoff for diagnosing cirrhosis [20]. This finding is in line with the observation that cirrhosis is associated with QTc prolongation. The association between LS and QTc is not limited to QTc prolongation in cirrhosis, though being extended to QTc values within normal reference values and minor degrees of LS elevation. In fact, LS is an independent predictor of QTc value, together with female gender, age, and heart rate, all well-known factors associated to the length of QTc [21–23]. In support of this hypothesis, we performed an out-of-sample and an out-of-time validation, both confirming the prediction model. On this basis, we speculate that liver steatosis is not related to QTc per se but rather through the development of liver fibrosis, an expected outcome of longstanding NAFLD with high liver fat content [24]. This is in line with studies that demonstrated a complex dysregulation of cardiovascular system in liver cirrhosis, leading to the definition of a relatively novel clinical entity, the so-called cirrhotic cardiomyopathy [25]. QTc prolongation is a relevant part of this syndrome, being highly prevalent in patients affected by liver cirrhosis [26] and, again, potentially explained by the increased adrenergic activity [27]. In fact, β-blockers reduce QTc length, while stressful events prolong it [28].

In the present study, we also managed to demonstrate that LS, along with HR and age, is a predictor of QTc prolongation. This is clinically relevant because it might help in identifying a subset of patients affected by chronic liver diseases who are at higher risk for significant QTc prolongation; specifically, a prolonged QTc is more likely in elderly women with advanced chronic viral hepatitis, a profile to be kept in mind before prescribing drugs that may prolong the QT interval. It is true, however, that sudden cardiac death is a relatively rare event in the natural history of cirrhosis; therefore, the clinical relevance of QTc prolongation in CLD remains to be established.

6. Conclusion

In conclusion, our data support the hypothesis of an association between QTc length and severity of liver damage in chronic liver disease and warn that the degree of fibrosis progression might be a major confounder to be taken into account when analyzing the relationship between QTc length and fatty liver.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors have no conflict of interest to declare.

Authors’ Contributions

Mattia Bellan and Cristina Rigamonti contributed equally to this work.

Supplementary Materials

Table S1: distribution of cirrhosis and severe steatosis according to the etiology of liver disease. Liver cirrhosis was defined as liver stiffness = 13 kPa and severe steatosis as controlled attenuation parameter = 296 dB/m. Data are reported as number (row %). Abbreviations: CLD: chronic liver disease; NAFLD: nonalcoholic fatty liver disease. Table S2: differences of QTc values according to the etiology of liver disease, estimated fat liver content, and estimated degree of fibrosis. Liver cirrhosis is defined as liver stiffness = 13 kPa and severe steatosis for controlled attenuation parameter = 296 dB/m. *K-W* test. Abbreviations: CLD: chronic liver disease; NAFLD: nonalcoholic fatty liver disease. Table S3: differences between patients with prolonged and normal QTc. The table shows the differences according to the underlying cause of chronic liver disease. The continuous variables are shown as medians (IQR), while categorical
variables are shown as N (%). Abbreviations: BMI: body mass index; LS: liver stiffness; CAP: controlled attenuation parameter; QTc: corrected QT; CR: conditional risk. (Supplementary Materials)

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