Received: 2 November 2021 | Revised: 16 November 2021 | Accepted: 22 November 2021

DOI: 10.1111/anec.12925

ORIGINAL ARTICLE

WILEY

QTc interval prolongation in the patients with primary biliary cholangitis

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Funding information
The study was supported by the China National Natural Science Foundation (No. 81702119) and the Shaanxi Province National Natural Science Foundation (No. 2018JQ8031)

Abstract

Background: The QT interval prolongation was associated with fatal arrhythmias and cardiac death. However, there were not adequate data to clarify the situation of QT interval prolongation in primary biliary cholangitis (PBC) patients. The aim of this study was to clarify the rate and the associated risk factors of corrected QT (QTc) interval prolongation in PBC patients.

Methods: From January 2016 to December 2020, PBC patients were retrospectively enrolled. The rate of QTc interval prolongation was surveyed and the associated risk factors were clarified by univariate and multivariate analyses.

Results: Among the 189 PBC patients, 24.3% (46/189) had the QTc interval prolongation. The univariate analysis showed that age, Child-Pugh classification, creatinine, international normalized ratio (INR), and platelet (PLT) were associated with QTc interval prolongation in the PBC patients. The multivariate analysis further showed only age ($p = .028$) and Child-Pugh classification ($p = .035$) were the associated risk factors. It had the highest risk of QTc interval prolongation (as high as 64.3%) in the patients who were more than 62.5 years old and with Child-Pugh C.

Conclusion: The QTc interval prolongation was frequent in PBC patients, especially in the patients with decompensated cirrhosis. The rate of QTc interval prolongation was as high as 64.3% in the PBC patients who were more than 62.5 years old and classified as Child-Pugh C.

KEYWORDS
cardiac electrophysiological abnormalities, Child-Pugh classification, primary biliary cholangitis, QTc interval prolongation

1 | BACKGROUND

Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is regarded as a classic autoimmune disease characterized histologically by chronic nonsuppurative destruction of the interlobular bile ducts. When breakdown of immune tolerance is initiated, inflammatory reaction will lead to cholangiocellular damage and apoptosis. Once bile duct loss and cholestasis are established,

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secondary to retention of bile salts and other toxic compounds further perpetuates damage to biliary epithelial cells, subsequently to the liver (Talwalkar & Lindor, 2003). Based on it, the elevated levels of serum alkaline phosphatase (ALP)/γ-glutamyl transpeptidase (γ-GT) and positive anti-mitochondrial antibody (AMA) are present in PBC patients as the critical features for diagnosis (Heathcote, 2000; Lindor et al., 2009). The liver is the mainly involved organ in PBC. However, it has been increasingly reported for extrahepatic manifestations, including metabolic bone diseases, nephropathy, interstitial lung disease, pulmonary hypertension, and cardiac involvement (Bian et al., 2018; Leslie et al., 2003; Sakamaki et al., 2011; Shen et al., 2009).

Cardiac involvement is a serious fatal complication for PBC. Granulomatous inflammation was the histopathological basis for bile duct injury, and involved in myocardial damage as well (Fagan et al., 1983). The AMA, a specific antibody for PBC, potentially induced cytotoxic effect for myocardial tissues by cross-reacting with a Ca^{2+} channel protein (Matsumoto et al., 2012). Due to Ca^{2+} channel alteration and myocardial damage, the heart electrophysiological abnormality became the important aspect of cardiac involvement for PBC. The QT interval prolongation is one of pathological electrophysiological abnormality, leading to the extension of the ventricular vulnerable period and the decrease of ventricular fibrillation threshold (Elming et al., 2002). In addition, QT interval prolongation is closely related to fatal arrhythmias (including torsade de pointes ventricular tachycardia) (Wit, 2018) and sudden cardiac death (Priori et al., 2016). Earlier studies indicated that PBC patients had prolongation of the corrected QT (QTc) interval (Kempler et al., 1994). However, there were not adequate data to clarify the rate and the associated factors of QTc interval prolongation in PBC patients.

Herein, the rate of QTc interval prolongation were surveyed and the risk factors were analyzed among the PBC patients to enrich the data of cardiac dysfunction and figure out the characteristics of high-risk patients with QTc interval prolongation.

2 | METHODS

2.1 | Study design

This was a retrospective study. From January 1 2016 to December 31 2020, a total of 189 PBC patients were enrolled from the First Affiliated Teaching Hospital of medical college, which is the biggest general hospital under the direct administration of the Chinese Ministry of Health. Inclusion criteria: (i) age was more than 18 years old; (ii) patients were corresponding to the diagnosis of PBC. The diagnostic criteria for PBC were as follows: chronic cholestasis with elevated serum alkaline phosphatase and/or γ-glutamyl transpeptidase levels; Antimitochondrial antibody (AMA) positivity and other histological features of the liver that are symbolic for diagnosis (Heathcote, 2000; Lindor et al., 2009). Exclusion criteria were if patients had other obstructive jaundice diseases; concomitant medication or surgical treatment associated with QT interval prolongation (Beach et al., 2018; Isbister et al., 2017; Kennelly & Esaian, 2013; Murphy & Dargie, 2007; Trinkley et al., 2013); heart disease causing QT intervals prolongation independently (including myocarditis; primary myocardiopathy; valvular heart disease and acute coronary syndrome); bundle-branch block or nonspecific ventricular conduction delay with QRS duration ≥120 ms; history of diabetes; cardiac arrest, or emergency treatment. This study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University (No. 2020.055).

Using an electronic medical record system, paper charts, and telephone interview, pertinent data from the services of the First Affiliated Hospital of Xi'an Jiaotong University were retrospectively reviewed and collected as follows: age, gender, diagnosis, duration of disease, treatment, 12-lead electrocardiogram (ECG), liver and renal function, blood routine and electrolyte examination, autoantibodies, and myocardial enzyme.

2.2 | Assessments and outcomes

The hepatic compensatory function is evaluated by Child-Pugh score. Child-Pugh classification A is considered as compensatory status (<5 points), Child-Pugh classification B (5–15 points), and C (>15 points) indicate decompensated cirrhosis (Liaw et al., 2004).

A 12-lead electrocardiogram (ECG) at 25 mm/s was obtained. Mean QT intervals for the entire ECG were corrected for heart rate using Bazzet's formula (QTc = QT/√RR interval) to obtain the QTc mean (Zareba & Lin, 2003). QTc prolongation was defined as ≥450 ms in men and ≥460 ms in women (Ramos-Rios et al., 2010). All ECGs were reviewed by two cardiologists with more than 15 years of experience.

The primary outcome was the rate of QTc interval prolongation in the PBC patients. The secondary outcomes were as follows: (i) The associated factors of QTc interval prolongation in the PBC patients; (ii) the rate of cardiac electrophysiological abnormalities involvement in the PBC patients.

2.3 | Statistical analysis

Quantitative data of normal distribution were expressed by mean ± standard deviation (SD) and were compared using the independent samples *t*-test. Quantitative data of non-normal distribution were expressed by median and range, and were compared using the independent samples Mann–Whitney *U*-test. Qualitative data were expressed by absolute count and percentage, and were compared using $\chi 2$ test. Univariate and multivariate logistic regression analyses were used to determined odds ratios (OR) and their 95% confidence intervals (CI) to the variables. Receiver operating

characteristic (ROC) curves and Youden Index were used to identify the optimal level of prediction. p value < .05 was considered statistically significant. The analyses were performed with SPSS software 13.0 (SPSS Inc).

3 | RESULTS

3.1 | Basic characteristics of the PBC patients

A total of 189 PBC patients were enrolled. The basic characteristics of them were shown in Table 1. The median age was 60 (20–84) years old. Among the 189 patients, 78.3% (148/189) were female, 46% (87/189) had decompensated cirrhosis and 3.7% (7/189) were combined with cardiac electrophysiological abnormalities.

TABLE 1 Demographics and basic characteristics of PBC patients

Variable	Value (N = 189)
Age, years[a]	60 (20–84)
Gender, female (%)	148 (78.3)
Decompensated cirrhosis, N (%)	87 (46.0)
Child-Pugh score[a]	6 (5–12)
Child-Pugh classification, N (%)	
Child-Pugh A	102 (54.0)
Child-Pugh B	56 (29.6)
Child-Pugh C	31 (16.4)
Cardiac electrophysiological abnormalities, N (%)	7 (3.7)
Hypertension, N (%)	23 (12.2)
ALT (U/L)[a]	35.0 (6.0–1170.0)
TBil (μmol/L)[a]	27.7 (5.9–451.2)
Albumin (g/L)[a]	34.7 (21.1–61.4)
TBA (μmol/L)[a]	49.7 (3.2–347.2)
CRE (μmol/L)[a]	51.0 (23.0–263.0)
BUN (mmol/L)[a]	4.8 (2.1–38.6)
INR[a]	1.12 (0.84–2.20)
HGB (g/L)[a]	108.0 (40.0–141.0)
WBC (10^9/L)[a]	3.4 (1.4–23.0)
PLT (10^9/L)[a]	82.0 (17.0–329.0)
K^+ (mmol/L)[a]	3.6 (2.2–7.2)
Ca^{2+} (mmol/L)[a]	2.1 (1.8–2.8)
Mg^{2+} (mmol/L)[a]	0.9 (0.6–1.8)
CK (U/L)[a]	60.0 (6.0–789.0)
CK-MB (U/L)[a]	20.0 (3.0–196.0)

Abbreviations: ALT, alanine aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase isoenzyme-MB; CRE, creatinine; HGB, hemoglobin; INR, international normalized ratio; PBC, primary biliary cholangitis; PLT, platelet; TBA, total bile acid; TBil, total bilirubin; WBC, white blood cell.

[a]The values were expressed as the median (range).

3.2 | QTc interval prolongation in PBC patients

Among the 189 PBC patients, 24.3% (46/189) had QTc interval prolongation. Twenty-one percent (32/148) were the female patients [the median QTc interval, 473 (460–547) ms] and 34.1% (14/41) were the male patients [the median QTc interval, 464 (452–520) ms].

As shown before, 46% (87/189) patients had decompensated cirrhosis. Compared with the patients without decompensated cirrhosis, the rate of QTc interval prolongation was much higher in those patients with decompensated cirrhosis (33.3% vs. 16.7%, $\chi^2 = 7.082$, $p = .008$, Figure 1). Moreover, the time of QTc interval was longer in the decompensated cirrhosis patients [442 (305, 535) vs. 433 (320, 547) ms, $Z = -2.467$, $p = .014$].

3.3 | Cardiac electrophysiological abnormalities involvement in PBC patients

Cardiac electrophysiological abnormalities were documented in seven patients (3.7%). Forty-three percent (2/46) were in the patients with QTc interval prolongation and 3.5% (5/143) were in the subjects without QTc interval prolongation (4.3% vs. 3.5%, $\chi^2 = 0.071$, $p = .678$), including premature ventricular contraction (2.2% vs. 0.7%), premature atrial contractions (2.2% vs. 1.4%), atrial fibrillation (0% vs. 1.4%).

3.4 | The associated factors of QTc interval prolongation in PBC patients

To identify the risk factors of QTc interval prolongation, the univariate and multivariate analyses were performed. The univariate analysis showed that age, Child-Pugh classification, CRE, INR, and PLT were associated with QTc interval prolongation in the PBC patients. Furthermore, multivariate analysis showed only age ($p = .028$) and Child-Pugh classification ($p = .035$) were the associated risk factors (Table 2).

Based on ROC analysis, the cut-off of age was determined. The cut-off of age was 62.5 years old, which had a sensitivity of 60.9%, specificity of 66.4%, and Youden index of 27.3% to predict the risk of QTc interval prolongation in the PBC patients. The area under ROC was 0.644 (95% CI, 0.560–0.728, $p = .003$, Figure 2a). As shown in Figure 2b, the PBC patients were divided into two groups due to whether age more than 62.5 years old. The proportions of QTc interval prolongation gradually increased with Child-Pugh classification in two groups. The patients more than 62.5 years old and with Child-Pugh C had the highest risk of QTc interval prolongation (as high as 64.3%).

4 | DISCUSSION

The prolongated QTc interval was associated with serious cardiac adverse events. It is limited for the data about QTc interval

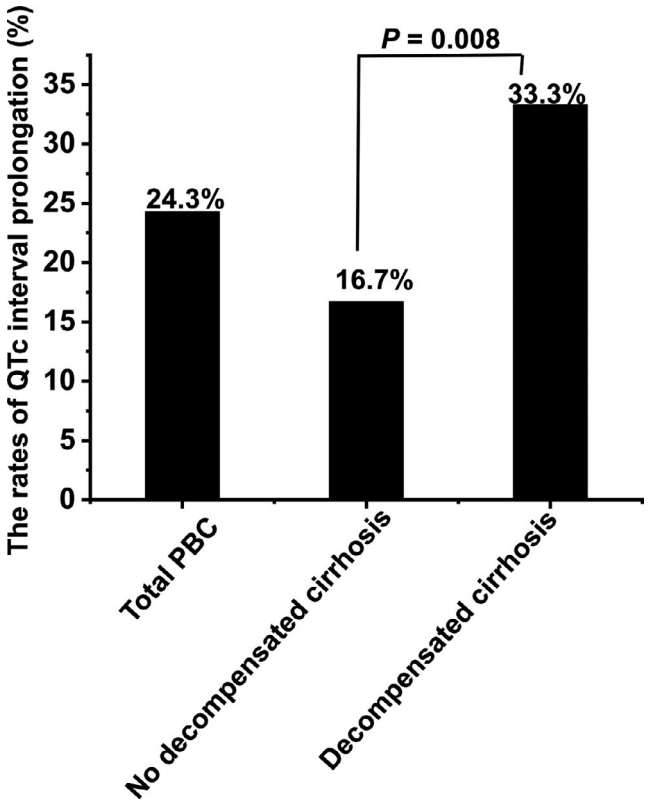

FIGURE 1 The rates of QTc interval prolongation in PBC patients. PBC, primary biliary cholangitis

prolongation among PBC patients. In this study, we surveyed the rate of QTc interval prolongation among the 189 PBC patients from 2016 to 2020 and clarified the associated risk factors. The rate of QTc interval prolongation was as high as 24.3% in the PBC patients. Moreover, old age and high Child-Pugh classification were closely associated with QTc interval prolongation. According to our knowledge, this is the first report, showing that it had high risk of QTc interval prolongation in the PBC patients who were more than 62.5 years old and classified as Child-Pugh C.

The QTc interval prolongation can be relied on as a risk factor for predicting imminent arrhythmias and associated with all-cause mortality (Arya et al., 2020; Bruyne et al., 1999). In our study, 24.3% of the PBC patients had QTc interval prolongation and 3.7% had cardiac electrophysiological abnormalities, including premature ventricular contraction, premature atrial contractions, and atrial fibrillation. Cardiac involvement was a rare complication of PBC, which reported to be presented in 4% of PBC patients, including myocardiopathy and cardiac electrophysiological abnormalities (Bian et al., 2018). Due to moderate sample size in this study, the rates of cardiac electrophysiological abnormalities had no statistic difference between the patients with or without QTc interval prolongation. However, based on the previous studies (Arya et al., 2020; Bruyne et al., 1999), it is suggested that the risk of cardiac dysfunction was high in the PBC patients with QTc interval prolongation.

TABLE 2 Clinical correlates of QTc interval prolongation by univariate and multivariate analyses in the PBC patients

Clinical characteristic	Univariate OR (95% CI) *p* value	Multivariate OR (95% CI) *p* value
Age, years	1.052 (1.015, 1.090) .006	**1.046 (1.005, 1.088) .028**
Gender, male	1.851 (0.904, 3.790) .092	
Child-Pugh classification	2.331 (1.499, 3.624) <.001	**1.880 (1.044, 3.387) .035**
ALT (U/L)	0.998 (0.995, 1.002) .316	
TBil (μmol/L)	1.001 (0.997, 1.005) .573	
Albumin (g/L)	0.975 (0.928, 1.025) .975	
TBA (μmol/L)	0.999 (0.995, 1.004) .756	
CRE (μmol/L)	1.019 (1.005, 1.034) .010	1.013 (1.000, 1.026) .056
BUN (mmol/L)	1.087 (0.984, 1.201) .102	
INR	11.753 (2.894, 47.725) .001	2.731 (0.443, 16.855) .279
HGB (g/L)	0.998 (0.983, 1.012) .734	
WBC (10^9/L)	1.102 (0.995, 1.220) .061	
PLT (10^9/L)	0.993 (0.987, 0.999) .034	0.999 (0.992, 1.005) .697
K^+ (mmol/L)	0.793 (0.434, 1.452) .453	
Ca^{2+} (mmol/L)	2.881 (0.396, 20.944) .296	
Mg^{2+} (mmol/L)	0.419 (0.043, 4.101) .454	
CK (U/L)	1.007 (0.999, 1.015) .068	
CK-MB (U/L)	0.996 (0.976, 1.016) .695	

Note: Abbreviations: ALT, alanine aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CK-MB, creatine kinase isoenzyme-MB; CRE, creatinine; HGB, hemoglobin; INR, international normalized ratio; OR, odds ratio; PBC, primary biliary cholangitis; PLT, platelet; TBA, total bile acid; TBil, total bilirubin; WBC, white blood cell.

Firstly, the univariate logistic regression analysis was used to determined the associated variables, then these variables ($p < .05$) were taken into the multivariate.

The heart function can be affected by the exacerbation of liver function. The QTc interval represents a measure of ventricular depolarization and repolarization, and its prolongation is associated with ventricular arrhythmias as well as sudden cardiac death. It has reported that the rates of QTc interval prolongation were 38.2% in the liver cirrhosis patients (Zhao et al., 2016) and 51% in the

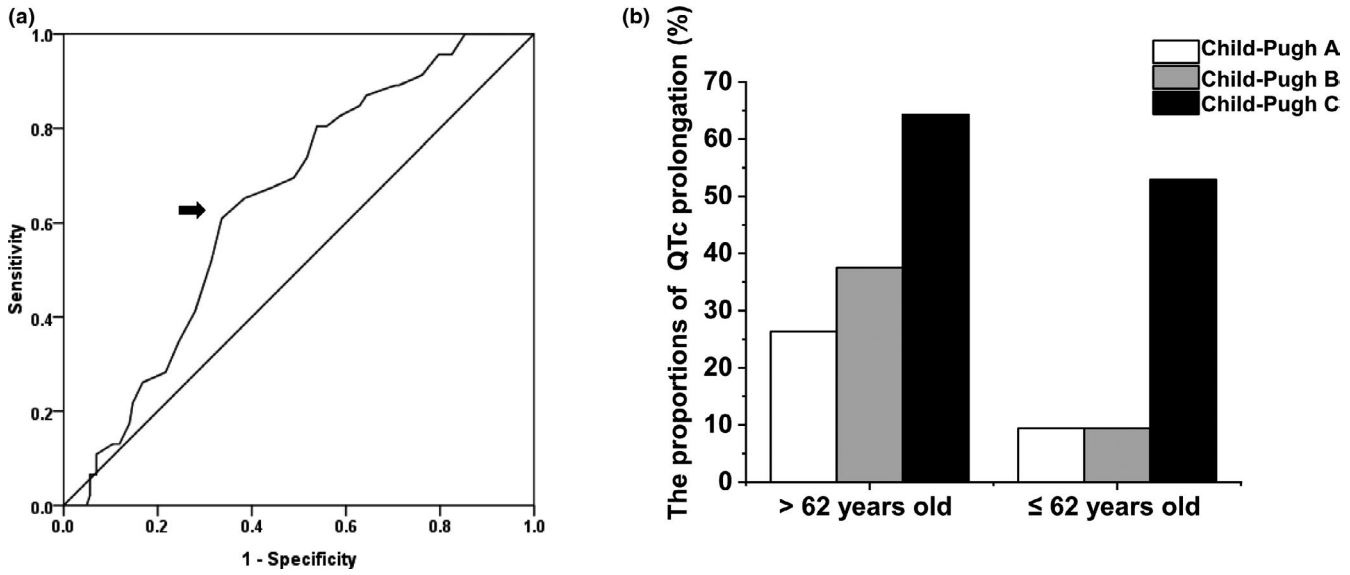

FIGURE 2 The effect of Age and Child-Pugh classification on QTc interval prolongation. (a) The ROC curve of age to predict the risk of QTc interval prolongation; (b) The proportions of QTc interval prolongation in the patients with different age and Child-Pugh classification

end stage liver disease patients (Kim et al., 2017), respectively. Multiple factors involved in liver diseases were thought to be responsible for the QTc interval prolongation, including bilirubin levels, bile acids levels, gonadal hormone alteration, electrolyte abnormalities, and autonomic imbalance with sympathetic nervous system hyperactivity (Bernardi et al., 1998; Oka et al., 1994; Schooling et al., 2014; Vasavan et al., 2018). Consistent with these studies, in our study, the patients with decompensated cirrhosis had a much higher risk of QTc interval prolongation compared with the patients without decompensated cirrhosis (33.3% vs. 16.7%, $p = 0.008$). Moreover, 34.1% male patients had prolonged QTc interval, which was higher compared with the female patients (34.1% vs. 21.6%), although there was no statistic difference. It is still elusive about the effect of gender hormone on the QTc interval prolongation. Kim et al. reported a much higher prevalence of QTc prolongation among males with end stage liver disease (Kim et al., 2017). However, Adigun et al. demonstrated that gonadal hormone concentrations had no effect on the QTc interval (Adigun et al., 2005). We performed the univariate and multivariate analyses and showed that age and Child-Pugh classification were associated with QT prolongation. The QTc interval prolongation was common in the elderly (Bruyne et al., 1999). The severity of liver dysfunction was considered as an important factor related to QTc interval (Zhao et al., 2016). A total of 5 components of Child-Pugh score, including hepatic encephalopathy, ascites, prothrombin activity, ALB, and bilirubin, directly or indirectly correlated with prolonged QTc interval. Our data showed the patients more than 62.5 years old and with Child-Pugh C had the highest risk of QTc interval prolongation (as high as 64.3%).

Here, the prevalence of QTc interval prolongation was surveyed in the PBC patients and the associated risk factors were clarified. Although the numbers of patients were moderate, a prospective well-designed cohort study with large sample size is necessary to evaluate the relationship between QTc interval and arrhythmia. The underling mechanism should be further studied.

In conclusion, QTc interval prolongation was frequent in PBC (24.3%), especially in the patients with decompensated cirrhosis. The rate of QTc interval prolongation was as high as 64.3% in the PBC patients who were more than 62.5 years old and classified as Child-Pugh C.

ACKNOWLEDGMENTS

The authors thank all individuals who have participated in this study. The authors thank Prof. Jinfeng Liu for their support and help in this study and Dr. Jiquan Liu for editing a draft of this manuscript.

CONFLICT OF INTEREST

All the authors declare that they have no competing interests, and all authors confirm its accuracy.

AUTHOR CONTRIBUTIONS

JW and LH conceived of the presented idea. ZW, RQ, BJ, and YW acquired data in the study. LM, PW, and NH analyzed data. ZW and JW drafted the article, and all authors discussed the results and contributed to the final manuscript.

ETHICAL APPROVAL

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (No. 2019.013).

DATA AVAILABILITY STATEMENT

The data in this study are available from the corresponding author on reasonable request.

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REFERENCES

Adigun, A. Q., Pinto, A. G., Flockhart, D. A., Gorski, J. C., Li, L., Hall, S. D., & Chalasani, N. (2005). Effect of cirrhosis and liver transplantation on the gender difference in QT interval. *American Journal of Cardiology*, *95*(5), 691–694. https://doi.org/10.1016/j.amjcard.2004.10.054

Arya, S., Kumar, P., Tiwari, B., Belwal, S., Saxena, S., & Abbas, H. (2020). What every intensivist should know about impairment of cardiac function and arrhythmias in liver disease patients: A review. *Indian Journal of Critical Care Medicine*, *24*(12), 1251–1255. https://doi.org/10.5005/jp-journals-10071-23695

Beach, S. R., Celano, C. M., Sugrue, A. M., Adams, C., Ackerman, M. J., Noseworthy, P. A., & Huffman, J. C. (2018). QT prolongation, torsades de pointes, and psychotropic medications: A 5-year update. *Psychosomatics*, *59*(2), 105–122. https://doi.org/10.1016/j.psym.2017.10.009

Bernardi, M., Calandra, S., Colantoni, A., Trevisani, F., Raimondo, M. L., Sica, G., Schepis, F., Mandini, M., Simoni, P., Contin, M., & Raimondo, G. (1998). Q-T interval prolongation in cirrhosis: Prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology*, *27*(1), 28–34. https://doi.org/10.1002/hep.510270106

Bian, S., Chen, H., Wang, L., Fei, Y., Yang, Y., Peng, L., Li, Y., & Zhang, F. (2018). Cardiac involvement in patients with primary biliary cholangitis: A 14-year longitudinal survey-based study. *PLoS One*, *13*(3), e0194397. https://doi.org/10.1371/journal.pone.0194397

de Bruyne, M. C., Hoes, A. W., Kors, J. A., Hofman, A., van Bemmel, J. H., & Grobbee, D. E. (1999). Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *European Heart Journal*, *20*(4), 278–284. https://doi.org/10.1053/euhj.1998.1276

Elming, H., Brendorp, B., Kober, L., Sahebzadah, N., & Torp-Petersen, C. (2002). QTc interval in the assessment of cardiac risk. *Cardiac Electrophysiology Review*, *6*(3), 289–294. https://doi.org/10.1023/a:1016345412555

Fagan, E. A., Moore-Gillon, J. C., & Turner-Warwick, M. (1983). Multiorgan granulomas and mitochondrial antibodies. *New England Journal of Medicine*, *308*(10), 572–575. https://doi.org/10.1056/NEJM198303103081006

Heathcote, E. J. (2000). Management of primary biliary cirrhosis. The American Association for the Study of Liver Diseases practice guidelines. *Hepatology*, *31*(4), 1005–1013. https://doi.org/10.1053/he.2000.5984

Isbister, G. K., Brown, A. L., Gill, A., Scott, A. J., Calver, L., & Dunlop, A. J. (2017). QT interval prolongation in opioid agonist treatment: Analysis of continuous 12-lead electrocardiogram recordings. *British Journal of Clinical Pharmacology*, *83*(10), 2274–2282. https://doi.org/10.1111/bcp.13326

Kempler, P., Varadi, A., Kadar, E., & Szalay, F. (1994). Autonomic and peripheral neuropathy in primary biliary cirrhosis: Evidence of small sensory fibre damage and prolongation of the QT interval. *Journal of Hepatology*, *21*(6), 1150–1151. https://doi.org/10.1016/S0168-8278(05)80640-3

Kennelly, C., & Esaian, D. (2013). Drug-induced cardiovascular adverse events in the intensive care unit. *Critical Care Nursing Quarterly*, *36*(4), 323–334. https://doi.org/10.1097/CNQ.0b013e3182a10c2a

Kim, S. M., George, B., Alcivar-Franco, D., Campbell, C. L., Charnigo, R., Delisle, B., Hundley, J., Darrat, Y., Morales, G., Elayi, S.-C., & Bailey, A. L. (2017). QT prolongation is associated with increased mortality in end stage liver disease. *World Journal of Cardiology*, *9*(4), 347–354. https://doi.org/10.4330/wjc.v9.i4.347

Leslie, W. D., Bernstein, C. N., Leboff, M. S., & American Gastroenterological Association Clinical Practice Committee. (2003). AGA technical review on osteoporosis in hepatic disorders. *Gastroenterology*, *125*(3), 941–966. https://doi.org/10.1016/S0016-5085(03)01062-X

Liaw, Y. F., Sung, J. J., Chow, W. C., Farrell, G., Lee, C.-Z., Yuen, H., Tanwandee, T., Tao, Q.-M., Shue, K., Keene, O. N., Dixon, J. S., Gray, D. F., & Sabbat, J. (2004). Lamivudine for patients with chronic hepatitis B and advanced liver disease. *New England Journal of Medicine*, *351*(15), 1521–1531. https://doi.org/10.1056/NEJMoa033364

Lindor, K. D., Gershwin, M. E., Poupon, R., Kaplan, M., Bergasa, N. V., & Heathcote, E. J. (2009). Primary biliary cirrhosis. *Hepatology*, *50*(1), 291–308. https://doi.org/10.1002/hep.22906

Matsumoto, K., Tanaka, H., Yamana, S., Kaneko, A., Tsuji, T., Ryo, K., Sekiguchi, K., Kawakami, F., Kawai, H., & Hirata, K.-I. (2012). Successful steroid therapy for heart failure due to myocarditis associated with primary biliary cirrhosis. *Canadian Journal of Cardiology*, *28*(4), 515.e3–515.e6. https://doi.org/10.1016/j.cjca.2011.12.010

Murphy, C. A., & Dargie, H. J. (2007). Drug-induced cardiovascular disorders. *Drug Safety*, *30*(9), 783–804. https://doi.org/10.2165/00002018-200730090-00005

Oka, H., Mochio, S., Sato, K., & Isogai, Y. (1994). Correlation of altered Q-T interval and sympathetic nervous system dysfunction in diabetic autonomic neuropathy. *European Neurology*, *34*(1), 23–29. https://doi.org/10.1159/000117003

Priori, S. G., Blomstrom-Lundqvist, C., Mazzanti, A., Blom, N., Borggrefe, M., Camm, J., Elliott, P. M., Fitzsimons, D., Hatala, R., Hindricks, G., Kirchhof, P., Kjeldsen, K., Kuck, K.-H., Hernandez-Madrid, A., Nikolaou, N., Norekvål, T. M., Spaulding, C., & Van Veldhuisen, D. J. (2016). 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Revista Española de Cardiología*, *69*(2), 176. https://doi.org/10.1016/j.rec.2016.01.001

Ramos-Rios, R., Arrojo-Romero, M., Paz-Silva, E., Carballal-Calvo, F., Bouzón-Barreiro, J. L., Seoane-Prado, J., Codesido-Barcala, R., Crespí-Armenteros, A., Fernández-Pérez, R., López-Moríñigo, J. D., Tortajada-Bonaselt, I., Diaz, F. J., & de Leon, J. (2010). QTc interval in a sample of long-term schizophrenia inpatients. *Schizophrenia Research*, *116*(1), 35–43. https://doi.org/10.1016/j.schres.2009.09.041

Sakamaki, Y., Hayashi, M., Wakino, S., Fukuda, S., Konishi, K., Hashiguchi, A., Hayashi, K., & Itoh, H. (2011). A case of membranous nephropathy with primary biliary cirrhosis and cyclosporine-induced remission. *Internal Medicine*, *50*(3), 233–238. https://doi.org/10.2169/internalmedicine.50.4020

Schooling, C. M., Zhao, J., & Zhang, Y. (2014). The association of androgens with QT interval and heart rate in US men. *International Journal of Cardiology*, *177*(2), 592–594. https://doi.org/10.1016/j.ijcard.2014.08.146

Shen, M., Zhang, F., & Zhang, X. (2009). Primary biliary cirrhosis complicated with interstitial lung disease: A prospective study in 178 patients. *Journal of Clinical Gastroenterology*, *43*(7), 676–679. https://doi.org/10.1097/MCG.0b013e31818aa11e

Talwalkar, J. A., & Lindor, K. D. (2003). Primary biliary cirrhosis. *Lancet*, *362*(9377), 53–61. https://doi.org/10.1016/S0140-6736(03)13808-1

Trinkley, K. E., Page, R. L. 2nd, Lien, H., Yamanouye, K., & Tisdale, J. E. (2013). QT interval prolongation and the risk of torsades de pointes: Essentials for clinicians. *Current Medical Research and Opinion*, *29*(12), 1719–1726. https://doi.org/10.1185/03007995.2013.840568

Vasavan, T., Ferraro, E., Ibrahim, E., Dixon, P., Gorelik, J., & Williamson, C. (2018). Heart and bile acids - Clinical consequences of altered bile acid metabolism. *Biochimica et Biophysica Acta (BBA) - Molecular*

Basis of Disease, *1864*(4), 1345–1355. https://doi.org/10.1016/j.bbadis.2017.12.039

Wit, A. L. (2018). Afterdepolarizations and triggered activity as a mechanism for clinical arrhythmias. *Pacing and Clinical Electrophysiology*, *41*(8), 883–896. https://doi.org/10.1111/pace.13419

Zareba, W., & Lin, D. A. (2003). Antipsychotic drugs and QT interval prolongation. *Psychiatric Quarterly*, *74*(3), 291–306.

Zhao, J., Qi, X., Hou, F., Ning, Z., Zhang, X., Deng, H., Peng, Y., Li, J., Wang, X., Li, H., & Guo, X. (2016). Prevalence, risk factors and in-hospital outcomes of QTc interval prolongation in liver cirrhosis. *American Journal of the Medical Sciences*, *352*(3), 285–295. https://doi.org/10.1016/j.amjms.2016.06.012

How to cite this article: Wang, Z., Qian, R., Wang, Y., Mo, L., Ju, B., Hu, N., Wang, P., He, L., & Wang, J. (2022). QTc interval prolongation in the patients with primary biliary cholangitis. *Annals of Noninvasive Electrocardiology*, 27, e12925. https://doi.org/10.1111/anec.12925