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META-ANALYSIS

Corrected QT interval in cirrhosis: A systematic review and meta-analysis

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Abstract

BACKGROUND

Corrected QT (QTc) interval is prolonged in patients with liver cirrhosis and has been proposed to correlate with the severity of the disease. However, the effects of sex, age, severity, and etiology of cirrhosis on QTc have not been elucidated. At the same time, the role of treatment, acute illness, and liver transplantation (Tx) remains largely unknown.

AIM

To determine the mean QTc in patients with cirrhosis, assess whether QTc is prolonged in patients with cirrhosis, and investigate whether QTc is affected by factors such as sex, age, severity, etiology, treatment, acute illness, and liver Tx.

METHODS

In the present systematic review and meta-analysis, the searching protocol "{[QTc] OR [QT interval] OR [QT-interval] OR [Q-T syndrome]} AND {[cirrhosis] OR [Child-Pugh] OR [MELD]}" was applied in PubMed, EMBASE, and Google Scholar databases to identify studies that reported QTc in patients with cirrhosis and published after 1998. Seventy-three studies were considered eligible. Data concerning first author, year of publication, type of study, method used, sample size, mean age, female ratio, alcoholic etiology of cirrhosis ratio, Child-Pugh A/B/C ratio, mean model for end-stage liver disease (MELD) score, treatment with β-blockers, episode of acute gastrointestinal bleeding, formula for QT correction, mean pulse rate, QTc in patients with cirrhosis and controls, and QTc according to etiology of cirrhosis, sex, Child-Pugh stage, MELD score, and liver Tx status (pre-Tx/post-Tx) were retrieved. The Newcastle-Ottawa quality assessment scale appraised the quality of the eligible studies. Effect estimates, expressed as proportions or standardized mean differences, were combined using the random-effects, generic inverse variance method of DerSimonian and Laird. Subgroup, sensitivity analysis, and meta-regressions were applied to assess heterogeneity.

The study has been registered in the PROSPERO database (CRD42023416595).

RESULTS

QTc combined mean in patients with cirrhosis was 444.8 ms [95% confidence interval (CI): 440.4-449.2; $P < 0.001$ when compared with the upper normal limit of 440 ms], presenting high heterogeneity ($I2 = 97.5\%$; 95%CI: 97.2%-97.8%); both Egger's and Begg's tests showed non-significance. QTc was elongated in patients with cirrhosis compared with controls ($P < 0.001$). QTc was longer in patients with Child-Pugh C cirrhosis when compared with Child-Pugh B and A ($P < 0.001$); Child-Pugh B patients presented longer QTc when compared with Child-Pugh A patients ($P = 0.003$). The MELD score was higher in patients with cirrhosis with QTc > 440 ms when compared with QTc ≤ 440 ms ($P < 0.001$). No correlation of QTc with age ($P = 0.693$), sex ($P = 0.753$), or etiology ($P = 0.418$) was detected. β-blockers shortened QTc ($P< 0.001$). QTc was prolonged during acute gastrointestinal bleeding ($P = 0.020$). Tx tended to improve QTc ($P < 0.001$). No other sources of QTc heterogeneity were revealed.

CONCLUSION

QTc is prolonged in cirrhosis independently of sex, age, and etiology but is correlated with severity and affected by β-blockers and acute gastrointestinal bleeding. QTc is improved after liver Tx.

Key Words: Liver cirrhosis; Corrected QT interval; Child-Pugh stage; Model for end-stage liver disease score; Liver transplantation; Meta-analysis

Core Tip: Corrected QT (QTc) interval is prolonged in patients with liver cirrhosis and has been proposed to correlate with the severity of the disease. The QTc upper normal limit in cirrhosis is widely debated. Moreover, the effects of sex, age, Child-Pugh stage, model for end-stage liver disease score, and etiology of cirrhosis have not been elucidated, while the role of liver transplantation has been largely unknown. The present study is the first systematic review and meta-analysis focusing on the topics mentioned above, thus aiming to determine whether QTc interval is a useful, easy, and inexpensive tool in the assessment of liver cirrhosis by clinicians.

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INTRODUCTION

The prolongation of ventricular repolarization, as reflected in rate-corrected QT (QTc) electrocardiogram interval, was first reported in 44% of patients with cirrhosis of alcoholic etiology[1,2]. QTc prolongation was soon recognized as a frequent electrocardiographic abnormality in patients with cirrhosis, regardless of the subsequent etiology[3,4]. QTc prolongation has been historically attributed to a broad spectrum of pathophysiological mechanisms involving electrolyte imbalance, sympathetic nervous system hyperactivity, portal hypertension, elevated bile salt plasma concentrations, direct alcohol toxicity, regimens such as β-blockers and diuretics, and stressful events such as acute gastrointestinal bleeding[1,3,5-10]. However, QTc prolongation is currently considered to reflect delayed ventricular repolarization in the presence of cirrhotic cardiomyopathy, an entity characterized mainly by ventricular diastolic dysfunction associated with liver cirrhosis in the absence of other known cardiac disease[11-19]. Of note, some contradictory evidence support that QTc prolongation is independent of the structural and functional abnormalities that characterize cirrhotic cardiomyopathy[20]. Moreover, it is debatable whether taming the gonadal hormone metabolism in cirrhosis might blur QTc sex-dependence observed in patients without cirrhosis[21]. Interestingly, liver transplantation (Tx) has been demonstrated to at least partly restore prolonged QTc[4,21-25].

QTc prolongation > 440 ms has been correlated with shortened overall survival in cirrhosis[3,26,27]; however, there is contradictory evidence obscuring this proposal[28]. More commonly, QTc length has been considered to reflect the severity of the disease in terms of either Child-Pugh stage[26,29-37] or model for end-stage liver disease (MELD) score[27,37-40]. On the contrary, several studies support dissimilar conclusions[4,41-45]. Additionally, the direct (due to alcoholic cardiomyopathy) and indirect (due to the aggravated course of the disease) role of alcohol in QTc cirrhosis-linked prolongation is still debatable[1]. Whether QTc abnormalities are more pronounced in alcoholic cirrhosis has not been elucidated yet, as there is contradictory evidence either for[33,46] or against[24,25,47] that possibility. Finally, QTc sex dependence might be less evident or even absent in patients with cirrhosis[3,21,23,25,30,38-41].

The present systematic review and meta-analysis was conducted to provide further evidence regarding a potential correlation between QTc length in patients with cirrhosis and age, sex, etiology of cirrhosis, severity of the disease in terms of Child-Pugh stage, and MELD score, treatment with β-blockers, episode of acute gastrointestinal bleeding, as well

as liver Tx by identifying all relevant studies and summarizing their results.

MATERIALS AND METHODS

Literature search

The study was conducted following Preferred Reporting in Systematic and Meta-Analysis (PRISMA) guidelines[48]. We used the PubMed and EMBASE databases to identify studies that reported QTc in patients with cirrhosis and were published between January 1998 and April 2023. We also utilized the Google Scholar database to retrieve any additional published or unpublished data, such as conference proceedings and other grey literature. We performed an iterative search until we could trace no additional publications. Moreover, a search for unpublished dissertations as well as other unpublished work was completed. The literature search was performed by both authors (Papadopoulos VP and Mimidis K). The study has been registered in the PROSPERO database (CRD42023416595); PROSPERO data were revised on August 8, 2023[49].

Study selection

The present systematic review was conducted following a search strategy that included the terms {[QTc] OR [QT interval] OR [QT-interval] OR [Q-T syndrome]} AND {[cirrhosis] OR [Child-Pugh] OR [MELD]}. Pre-specified eligibility criteria used the PICO strategy [P: Populations/people/patient/problem: Patients who have cirrhosis and healthy individuals (controls), I: Intervention(s): Liver Tx, C: Comparison: QTc in (1) Patients with cirrhosis *vs* upper normal limit; (2) Patients with cirrhosis *vs* controls; (3) Males with cirrhosis *vs* females with cirrhosis; (4) Patients with cirrhosis of Child-Pugh stage A *vs* B *vs* C; (5) Patients with cirrhosis of alcoholic etiology *vs* viral etiology; (6) Relation with age; (7) Relation with MELD score; (8) Patients with cirrhosis before *vs* after liver Tx; (9) Relation with β-blockers; (10) Relation with episode of acute gastrointestinal bleeding; and (11) Relation with age, sex, and etiology of cirrhosis in transplanted patients, O: Outcome: Combined mean, percentage; standardized mean difference (SMD)][50]. Exclusion criteria were: (1) Review articles, case reports, and letters; (2) Duplicated or overlapping studies (if that was the case, only the most recent or the highest level of study or the most informative study was included); and (3) Studies published only as abstracts. The process was performed independently by both authors. Mimidis K was responsible for resolving any discordance. The Cohen kappa statistic was preferred to assess the level of agreement between the two investigators. No software was used for study retrieval. Sources of financial support were traced where possible.

Data extraction

Data concerning first author, year of publication, type of study, method used, sample size, mean age, female ratio, alcoholic etiology of cirrhosis ratio, Child-Pugh A/B/C ratio, mean MELD score, use of β-blockers, formula for QT correction, mean pulse rate, QTc in patients with cirrhosis and controls, and QTc according to etiology of cirrhosis, sex, Child-Pugh stage, and Tx status (pre-Tx/post-Tx) were retrieved independently by both authors. Mimidis K supervised the process and resolved any potential discordance.

Risk of bias

Funnel plots assessed the risk of publication bias. Trim-and-fill analysis was used to impute missing studies in cases of significant publication bias. The Newcastle-Ottawa Scale (NOS) evaluated the risk of bias assessment of the eligible studies; scores ≥ 7-9, 4-6, and < 4 were considered to reflect low, intermediate, and high risk, respectively[51]. Furthermore, the GRADE assessment was used to evaluate evidence certainty rating risk of bias, imprecision, inconsistency, indirectness, publication bias, and effect size for every endpoint[52]. When comparing hazard ratios (HRs) between two groups, small, medium, and large effect sizes were considered to be approximately 1.3, 1.9, and 2.8, respectively[53].

Statistical analysis

Data were synthesized using MedCalc Statistical Software version 20.218 (MedCalc Software bv, Ostend, Belgium; https://www.medcalc.org; 2023). Effect estimates, expressed as QTc/upper normal limit percentage or SMD, were extracted from every study possible and combined using the random-effects, generic inverse variance method of DerSimonian and Laird[54], which assigned the weight of each study in the pooled analysis inversely to its variance. Combination of means and standard deviations (SDs) were performed using the freely available online tool located at https://www.statstodo.com/CombineMeansSDs.php. Means and estimates based on sample size, median, range, and interquartile range were calculated using the freely available online tool located at https://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html[55-57]. SD estimates were computed from the mean, confidence interval (CI), and sample size using the freely available online tool https://www.omnicalculator.com/statistics/confidence-interval. Effect size Cohen's *d* was calculated from 2^2 contingency data using the freely available online tool https://www.psychometrica.de/effect_size.html. The correlation coefficient was calculated for paired data using the formula $(SD_{baseline}^2 + SD_{final}^2 - SD_{change}^2)/(2 \times SD_{baseline} \times SD_{final})$. A subgroup analysis was performed to investigate the potential effect of hospitalization, comorbidities, and treatments affecting QT. Sensitivity analysis assessed the correlation coefficient *r* concerning pre-Tx and post-Tx status. HR was calculated from time-to-event data and log-rank *P* value as described elsewhere[58]. The NORMSINV function, freely available from MedCalc software, was used for that purpose. The formula $QT_{Bazett} = QT_{Fridericia} \times RR^{-1/6}$ was used to convert $QT_{Fridericia}$ (QTc corrected with the use of Fridericia formula) to QT_{Bazett} (QTc corrected with the use of

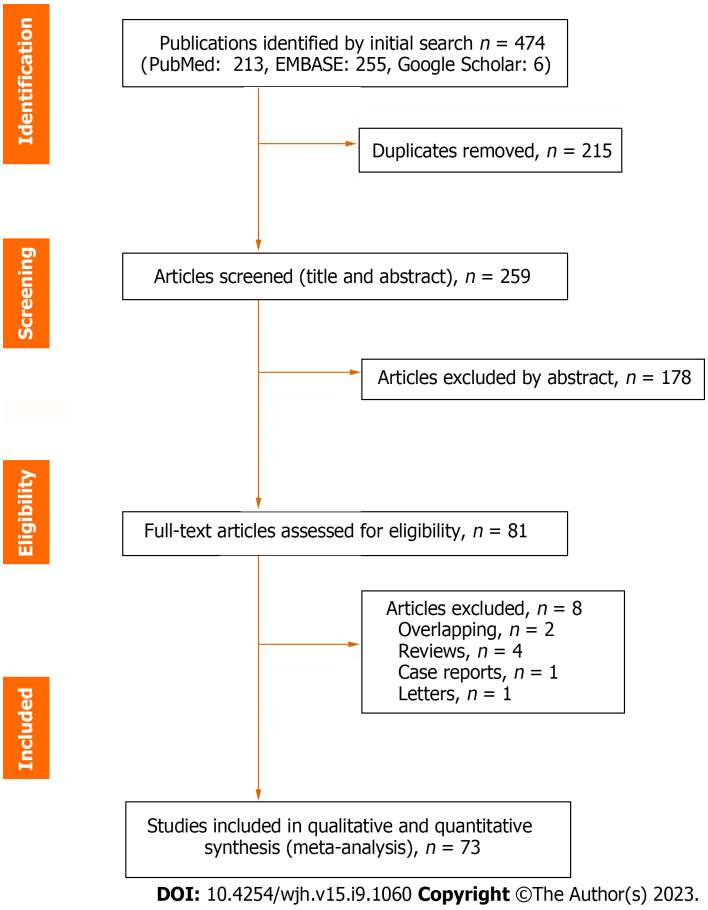

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Figure 1 Study selection.

Bazett formula) given that the mean heart rate was 60-100 beats/min. Heterogeneity was approached using the Q test and I^2 statistic; Q test P value < 0.10 was indicative of a statistically significant result. Furthermore, a value of $I^2 \leq 25\%$ was indicative of insignificant heterogeneity, 26%-50% of low heterogeneity, 51%-75% of moderate heterogeneity, and > 75% of high heterogeneity[59,60]. Heterogeneity was analyzed through meta-regressions and derived standardized coefficients beta (bSD) focusing separately on study characteristics and quality assessment. Multivariate analysis was omitted in cases where the available studies numbered less than 10. Meta-regressions were performed using SPSS 26.0 software (IBM Corp., Armonk, NY, United States). Synthesis of effect sizes was performed using the MedCalc® Statistical Software version 20.218 and Meta-Essentials Excel-based software[61].

RESULTS

Study selection

Four hundred and sixty-eight potentially relevant publications (PubMed: 213, EMBASE: 255, Google Scholar: 6) were identified. No unpublished data of interest were detected. The authors removed duplicates and critically appraised the title, the abstract, and the full text of the remaining publications (Figure 1). Finally, 73 studies, including 14495 patients, were eligible for qualitative and quantitative meta-analyses (Table 1)[3,4,6,7,10-15,17,18,21,23-47,62-96].

QTc interval in patients with cirrhosis

QTc was elongated in patients with cirrhosis when compared with controls (SMD = 1.187; 95%CI: 0.804-1.570; P < 0.001). The I^2 was 88.8% (95%CI: 81.0%-93.4%; P < 0.001) (Figure 2A). QTc combined mean in patients with cirrhosis (n = 7715) was 444.8 ms (95%CI: 440.4-449.2; P < 0.001 when compared with the upper normal limit of 440 ms), presenting high heterogeneity (I^2: 97.5%; 95%CI: 97.2%-97.8%; P < 0.001) (Figure 2B).

A subgroup analysis was performed to investigate the potential effect of hospitalization, comorbidities, and treatments affecting QT. Thus, when non-hospitalized patients with cirrhosis without any other comorbid condition or treatment with known effect of QT were considered (n = 1448), the QTc combined mean was 444.0 ms (95%CI: 437.8-450.1) with an I^2 of 92.4% (95%CI: 89.6%-94.5%; P < 0.001). When patients with cirrhosis who either might have been hospitalized or presented other comorbidities or were treated with regimens affecting QT were considered (n = 6267), the QTc combined mean was 445.3 ms (95%CI: 439.6-450.6) with an I^2 of 98.1% (95%CI: 97.9%-98.4%; P < 0.001). These two groups yielded comparable results (P = 0.823) (Supplementary Figures 1 and 2).

Table 1 Characteristics of eligible studies

Ref.	Type of study	Device	Formula	Patients, *n*	Controls, *n*	Female ratio	Alcoholic etiology ratio	Child-Pugh			MELD score	Age in yr	QTc									
								A, *n*	B, *n*	C, *n*				Prolongation ratio	Controls	Females	Viral etiology	Acohol etiology	Child-Pugh A	Child-Pugh B	Child-Pugh C	Tx pre	Tx post
Wang *et al*[62], 2023	R	E	B	1022		0.095	1					52.6 ± 11.6		0.107									
Bilous *et al*[10], 2023	P	H	B	33		0.394		8	14	11		48.0 ± 12.0	393.7 ± 35.0										
Barutcu *et al*[37], 2023	R	E	B	100	100	0.440		32	34	34	16 ± 8	60.0 ± 42.2	446.3 ± 49.3		439 ± 33				410 ± 23	455 ± 39	473 ± 53		
Lu *et al*[46], 2022	R	E	B	3529		0.233	0.182					55.0 ± 11.0		0.158									
Wang *et al*[63], 2022	R	E	B	189		0.783		102	56	31		59.4 ± 11.8	435.9 ± 46.1	0.243					433 ± 45	439 ± 47	439 ± 47		
Li *et al*[27], 2021	P	E	F	274		0.456		108	122	44	12 ± 4	61.8 ± 12.8		0.328									
Ou *et al*[40], 2021	R	E	B	167		0.281	0.168	70	81	16	11 ± 4	52.9 ± 10.8		0.665									
Ko *et al*[25], 2021	R	E	B	408		0.236	0.093					57.1 ± 12.0	452.0 ± 31.0	0.650								452 ± 31	430 ± 32
Héla *et al*[36], 2020	P	H	B	42		0.429	0.095	12	15	15		60.0 ± 13.2	435.9 ± 21.8	0.476					423 ± 19	429 ± 17	453 ± 17		
Abrahamovych *et al*[64], 2020	R	H	B	87		0.276	1					44.5 ± 4.3	443.8 ± 34.4										
Ibrahim *et al*[65], 2020	P	E	B	50		0.580	0	38	12	0		52.0 ± 12.0	415.8 ± 24.4										
Hussain *et al*[66],	P	E	B	87	87	0.460	0.316					47.0	470.0	0.218	400 ± 50								

2020											± 13.3	± 50.0										
Kim *et al*[35], 2020	R	E	B	310		0.274	0.274	105	94	111	46.0 ± 17.0	450.0 ± 43.0					460 ± 44	417 ± 29	452 ± 34	480 ± 38		
Toma *et al*[67], 2020	P	E	B	63		0.508	0	18	20	25	56.2 ± 13.5	452.5 ± 27.7	0.460			453 ± 28		445 ± 27	451 ± 23	459 ± 31		
Bhardwaj *et al*[68], 2020	P	E	B	100	100	0.150	0.530	4	35	61	49.8 ± 13.6	458.5 ± 27.0		424 ± 28								
Gaafar *et al*[69], 2019	P	E	B	112			0					424.4 ± 36.6										
Kazankov *et al*[28], 2019	R	E	B	915								415.0 ± 30.0										
Moaref *et al*[70], 2019	P	E	B	30		0.367				16 ± 5	41.0 ± 6.6											
Santeusanio *et al*[71], 2019	R	E	B	258		0.337	0.097			18 ± 10	59.5 ± 9.7	454.4 ± 27.9	0.403									
Biselli *et al*[72], 2019	R	E	F	474		0.352	0.236			13 ± 5	61.7 ± 12.6	438.0 ± 42.0										
Tieranu *et al*[45], 2018	P	E	B	60		0.433		6	28	26	59.4 ± 7.3	457.8 ± 23.9						456 ± 27	452 ± 26	462 ± 20		
Lee *et al*[39], 2018	R	E	B	283		0.247	0.113			17 ± 11	55.1 ± 7.7	449.9 ± 31.6	0.636								450 ± 32	435 ± 32
Hajiaghamohammadi *et al*[73], 2018	P	E	B	37		0.432		12	12	13	58.8 ± 11.5	418.5 ± 41.9										
Główczyńska *et al* [44], 2018	R	E	B	151		0.371	0.179	50	73	28	12 ± 5	49.0 ± 12.3	426.3 ± 41.6	0.338		426 ± 41	432 ± 45	423 ± 38	424 ± 46	438 ± 34		
Tahata *et al*[74], 2018	P	E	B	104		0.654		104	0	0		71.1 ± 8.4	415.9 ± 30.6					416 ± 31				

Tsiompanidis *et al* [75], 2018	P	E	B	51		0.373	0.333	22	18	11	28 ± 19	55.2 ± 14.2	428.1 ± 31.0	0.431				437 ± 31	419 ± 30	419 ± 30	435 ± 30		
Yap *et al*[43], 2018	R	E	B	148		0.527	0.155	17	57	9		72.4 ± 14.0	440.3 ± 45.6						464 ± 63	432 ± 33	448 ± 63		
Kim *et al*[76], 2017	R	E	B	406		0.404	0.389				18 ± 9	56.4 ± 9.0	454.5 ± 27.8	0.510									
Rimbaş *et al*[18], 2018	P	E	B	46	46	0.348	0.522	23	16	7	13 ± 5	57.0 ± 9.0	436.0 ± 30.0	0.413	404 ± 21			438 ± 35					
Salgado *et al*[42], 2016	P	E	B	67		0.478	0.239	25	26	16		54.0 ± 12.9	418.7 ± 26.6	0.224					415 ± 34	418 ± 21	426 ± 22		
Naqvi *et al*[34], 2016	P	E	B	89		0.438	0	17	29	43		51.5 ± 12.4	475.1 ± 73.3	0.461					420 ± 36	459 ± 56	508 ± 78		
Zhao *et al*[38], 2016	R	E	B	1268		0.347	0.253	497	528	140	6 ± 7	56.0 ± 12.1		0.382									
Sonny *et al*[77], 2016	R	E	B	106		0.280	0.179				17 ± 8	55.0 ± 9.0	453.0 ± 28.0									453 ± 28	442 ± 29
Barbosa *et al*[17], 2016	C	E	B	26		0.154	0.769	17	8	1	9 ± 5	54.6 ± 10.4	460.0 ± 23.0	0.769									
Carvalheiro *et al*[78], 2016	R	E	F	106		0.198	0.651	23	24	59	17 ± 8	54.8 ± 8.5		0.189									
Pourafkari *et al*[79], 2016	R	E	B	69		0.348	0.217	14	28	27	17 ± 7	56.8 ± 16.0	452.2 ± 46.0	0.507					453 ± 52	455 ± 40	449 ± 50		
Barakat *et al*[80], 2015	P	E	B	74		0.324	0				19 ± 26		473.1 ± 25.1										
Voiosu *et al*[81], 2015	P	E	F	74		0.378	0.378	43	12	19	13 ± 5	58.0 ± 11.0	418.3 ± 26.8										
Cichoż-Lach *et al*[82], 2015	R	E	B	122	32	0.344	0.664	28	40	54		42.1 ±	447.5 ±		394 ± 23		465 ± 50	443 ± 7	438 ± 35	434 ± 40	476 ± 40		

											12.7	29.9										
Peter *et al*[83], 2014	P	E	B	78	0.154	0.538				15 ± 5	51.2 ± 11.9	424.0 ± 10.2										
Moaref *et al*[15], 2014	P	E	B	80	0.375		0	0	80		41.0 ± 14.0	490.0 ± 51.0									490 ± 51	
Josefsson *et al*[84], 2014	R	E	B	202	0.307		22	91	89	17 ± 6	52.0 ± 11.0		0.262									
Karagiannakis *et al*[14], 2014	P	E	B	45	0.267	0.444	26	15	3	12 ± 4	57.2 ± 12.4	428.0 ± 27.5										
Yataco *et al*[41], 2014	R	E	B	17	0.471	0.235	0	1	16	29 ± 7	57.9 ± 7.9	461.4 ± 37.4	0.529		461 ± 38	459 ± 31	479 ± 42					
Bhatti *et al*[85], 2014	C	E	B	166	0.422	0	22	69	75		57.1 ± 12.0	429.9 ± 45.1	0.247									
Møller *et al*[86], 2012	P	E	B	10	0.500						55.6 ± 10.0	450.0 ± 20.0										
Trevisani *et al*[87], 2012	R	E	F	70	0.329	0.186				16 ± 1	61.7 ± 12.5	415.9 ± 36.0	0.243									
Zamirian *et al*[24], 2012	P	E	B	243	0.380	0.049						446.9 ± 12.5	0.432			483 ± 20	478 ± 25				447 ± 13	383 ± 49
Kim *et al*[88], 2011	P	E	B	100	0.140		18	48	34	14 ± 8	52.3 ± 8.3											
Shin *et al*[89], 2011	P	E	B	50	0.200		14	19	17		52.0 ± 7.0	433.2 ± 32.7	0.440									
Mozos *et al*[33], 2011	P	E	B	38	0.500	0.395	16	13	9		58.0 ± 12.0	493.0 ± 46.0	0.711			481 ± 51	527 ± 50	462 ± 25	493 ± 62	520 ± 45		
Vuppalanchi *et al*[90], 2011	P	E	B	14	0.286	0.500				11 ± 2	53.9 ± 9.6											

Møller *et al*[91], 2010	P	E	B	43		0.326	1	17	18	8	11 ± 3	57.4 ± 9.1	453.0 ± 31.0									
Zurick *et al*[23], 2010	R	E	B	269		0.372					21	50.9	448.3 ± 41.3	0.502		449 ± 11					449 ± 41	417 ± 41
Lossnitzer *et al*[13], 2010	P	E	B	20		0.450	0.600				15 ± 6	52.4 ± 9.4		0.250								
Genovesi *et al*[32], 2009	P	H	B	40		0.000	0.450	26	15	7		56.1 ± 11.2	439.3 ± 30.2	0.525					425 ± 24	452 ± 30	465 ± 24	
Zambruni *et al*[31], 2008	P	E	B	30		0.167	0.233	15	10	5	13 ± 1	58.8 ± 11.0	455.4 ± 26.8	0.367			459 ± 38	450 ± 38	440 ± 16	466 ± 26	486 ± 20	
Henriksen *et al*[92], 2007	P	E	B	48		0.354	0.917	15	19	14		52.1 ± 11.1	450.0 ± 33.9	0.563					441 ± 53	441 ± 39	470 ± 76	
Kosar *et al*[93], 2007	R	E	B	33		0.455		9	15	9		53.0 ± 11.0	412.5 ± 89.6						405 ± 51	411 ± 46	427 ± 64	
Hansen *et al*[12], 2007	P	H	B	23		0.261	0.609	6	10	7		55.0 ± 8.6	441.0 ± 31.7	0.478					420 ± 53	438 ± 48	461 ± 45	
Zuberi *et al*[94], 2007	C	E	B	78		0.269		6	19	53		34.4	438.0 ± 15.0	0.192								
Zambruni *et al*[47], 2007	P	E	B	100	53	0.370	0.210	34	39	27		57.2 ± 7.6	465.2 ± 33.3	0.520	416 ± 24							
Ytting *et al*[7], 2005	P	E	B	80		0.263	0.488	33	33	14		51.0 ± 10.4	447.0 ± 42.3	0.513								
Adigun *et al*[21], 2005	P	E	B	183		0.366	0.164	7	143	33		47.7 ± 7.4	419.6 ± 31.8	0.279		419 ± 35					436 ± 21	421 ± 21
Henriksen *et al*[95], 2004	P	E	B	24		0.125	1	3	12	9		58.3 ± 11.0	462.0 ± 40.3	0.583				462 ± 40				
Bal and Thuluvath [26], 2003	R	E	B	409		0.440	0.196	0	273	136		49.0 ±	439.4 ±	0.396				456 ± 42		434 ± 31	451 ± 43	450 ±	429 ± 29

											14.2	36.4										39	
Trevisani *et al*[6], 2003	P	E	B	19		0.474					61.2 ± 6.5	465.0 ± 26.2	0.842										
Mimidis *et al*[30], 2005	R	E	B	52		0.250	0.558	23	19	10	61.3 ± 11.1	466.6 ± 37.8	0.596		468 ± 15	466 ± 43	468 ± 15	446 ± 27	480 ± 39	489 ± 36		
Henriksen *et al*[11], 2002	P	E	B	24	17	0.125	1	3	12	9	58.3 ± 11.0	462.0 ± 40.3	0.375	410 ± 41			462 ± 40					
Puthumana *et al*[29], 2001	R	E	B	130		0.469		42	53	35	52.0 ± 10.0	442.7 ± 29.3	0.446					432 ± 23	443 ± 29	455 ± 33		
Quera *et al*[96], 2000	R	E	B	47								460.0 ± 30.0	0.723									
Bernardi *et al*[3], 1998	P	E	B	94	37	0.277	0.074	24	45	25	53.1 ± 13.6	440.3 ± 31.0	0.468	394 ± 36	444 ± 25		453 ± 25					
Finucci *et al*[4], 1998	P	E	B	75	24	0.360	0.453	23	37	15	57.0 ± 11.0	452.0 ± 33.0	0.600	414 ± 28			463 ± 31				449 ± 31	415 ± 26

C: Case-control; NOS: Newcastle-Ottawa scale; P: Prospective; R: Retrospective; E: Electrocardiography; B: Bazett's formula; H: Holter; F: Fridericia's formula; QTc: Corrected QT; MELD: Model for end-stage liver disease; Tx: Transplantation.

The pre-specified upper normal limit for QTc was higher for females (median: 440 ms; range: 440-470 ms) when compared with males (median: 440 ms; range: 420-462 ms). The related samples Wilcoxon signed rank test showed statistical significance ($P < 0.001$) (Figure 3).

Effect of sex and age on QTc interval

QTc was comparable between male and female patients (SMD = -0.032; 95%CI: -0.229 to 0.165; $P = 0.753$); I^2 was 78.5% (95%CI: 62.0%-87.8%; $P < 0.001$) (Figure 4A). Moreover, no correlation of QTc with age ($P = 0.974$) was detected, even after adjustment for alcoholic etiology rate and MELD score ($P_{adj} = 0.160$).

Effect of etiology of cirrhosis on QTc interval

Patients with cirrhosis of alcoholic etiology exhibited comparable QTc with those of viral etiology (SMD = 0.095; 95%CI: -0.109 to 0.264; $P = 0.418$). Heterogeneity was moderate (I^2: 47.8%; 95%CI: 0.0%-74.8%; $P = 0.045$) (Figure 4B).

Effect of Child-Pugh stage and MELD score on QTc interval

QTc was longer in patients with Child-Pugh C cirrhosis when compared with Child-Pugh A (SMD = 0.860; 95%CI: 0.547-

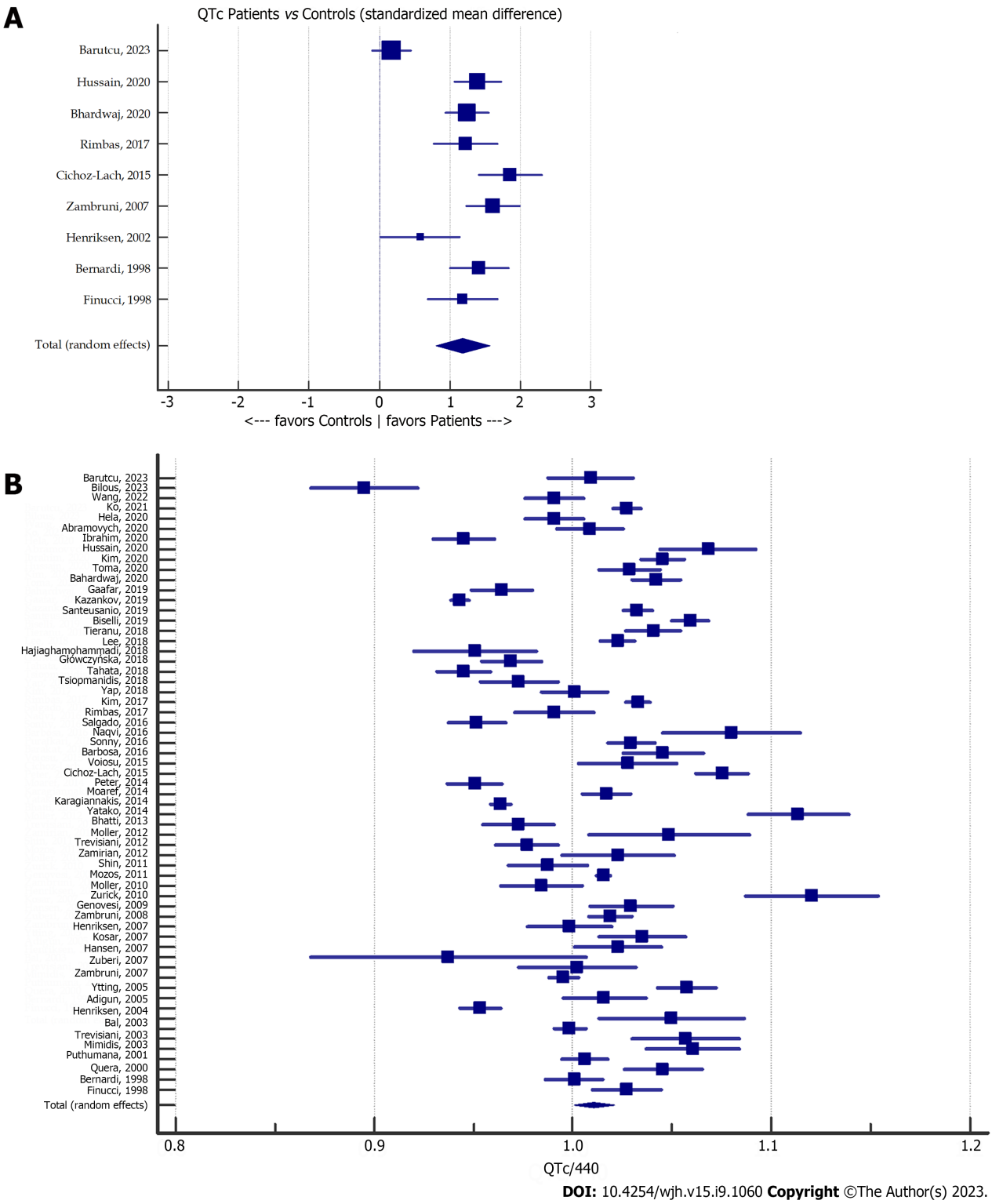

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Figure 2 Meta-analysis forest plot. A: Corrected QT (QTc) in patients with cirrhosis *vs* controls; B: QTc compared with the upper normal limit (440 ms) ratio in patients with cirrhosis. QTc: Corrected QT.

1.173; $P < 0.001$) and B (SMD = 0.474; 95%CI: 0.344-0.6003; $P < 0.001$); I^2 was 80.8% (95%CI: 71.5%-87.1%; $P < 0.001$) and 24.9% (95%CI: 0.0%-55.4%; $P = 0.647$), respectively (Figures 5A and B). Moreover, Child-Pugh B patients with cirrhosis were characterized by longer QTc when compared with Child-Pugh A patients (SMD = 0.372; 95%CI: 0.126-0.619; $P = 0.003$); I^2 was 76.0% (95%CI: 63.5%-84.2%; $P < 0.001$) (Figure 5C). Considering the effect of the Child-Pugh score on QTc, a significant dose-response gradient was observed using Spearman's non-parametric correlation coefficient (rho = 0.526, $P < 0.001$). The MELD score was higher in patients with cirrhosis with QTc > 440 ms when compared with patients with QTc ≤ 440 ms (SMD = 0.509; 95%CI: 0.249-0.769; $P < 0.001$); I^2 was 78.1% (95%CI: 47.4%-90.9%; $P = 0.001$) (Figure 6A).

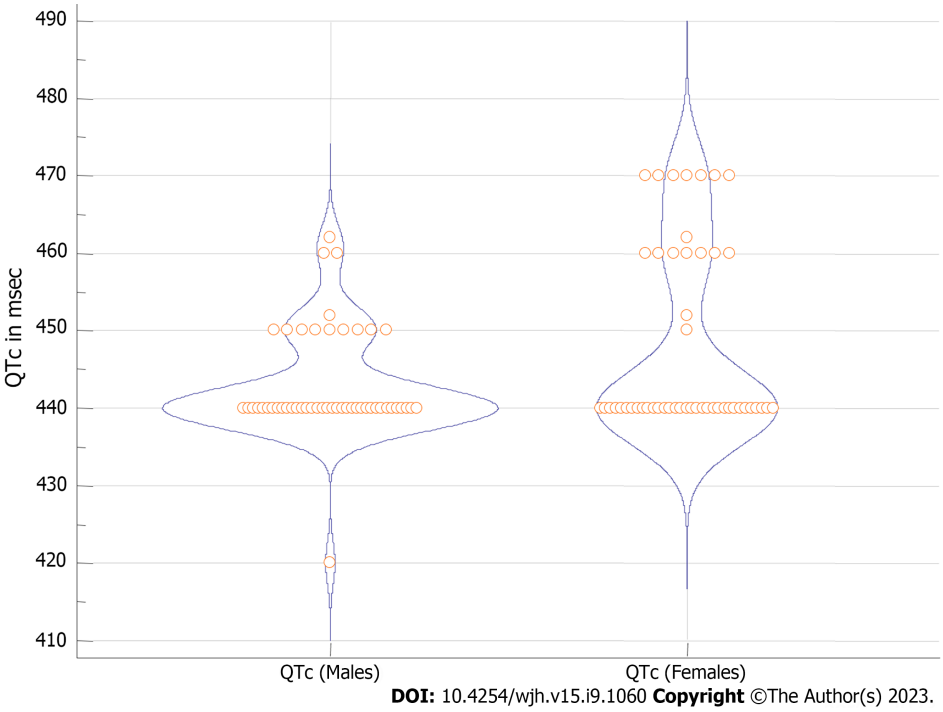

Figure 3 Violi plot for corrected QT upper normal limit used in the included studies. QTc: Corrected QT.

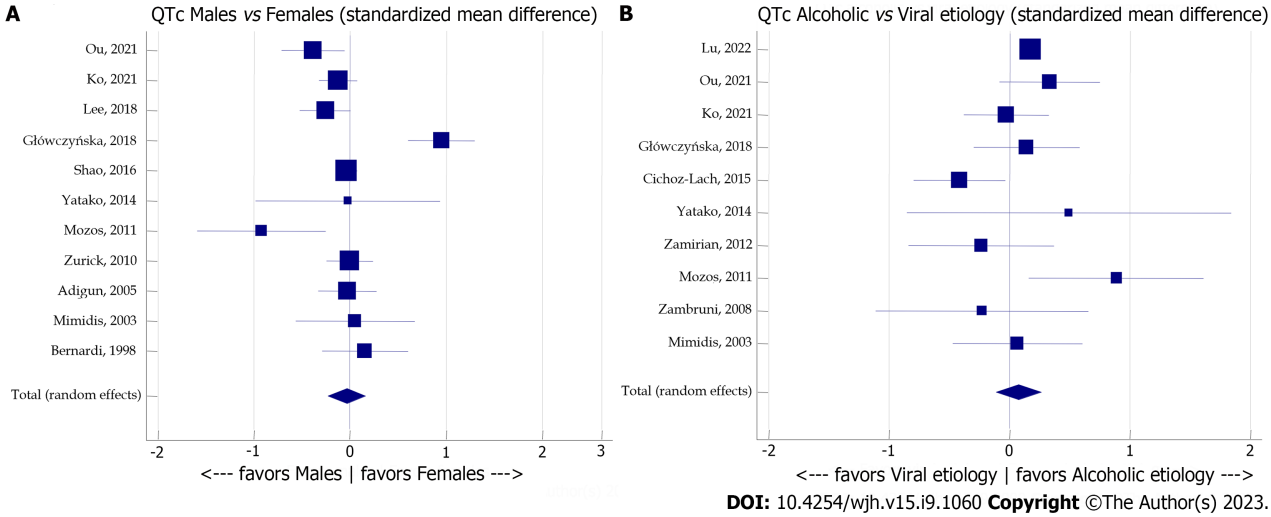

Figure 4 Meta-analysis forest plot concerning the effect of sex and etiology of cirrhosis on corrected QT. A: The effect of sex on corrected QT (QTc) in patients with cirrhosis; B: The effect of etiology of cirrhosis on QTc. QTc: Corrected QT.

Role of liver Tx regarding QTc interval

Liver Tx tended to improve QTc (pre-Tx *vs* post-Tx QTc SMD = 0.808; 95%CI: 0.488-1.129; $P < 0.001$). I^2 was 93.9% (95%CI: 90.1%-96.2%; $P < 0.001$) (Figure 6B). Since pre-Tx and post-Tx QTc values were correlated, the correlation coefficient r was 0.7, using two separate approaches: (1) Sensitivity analysis for $r = 0.1$ to $r = 0.9$ (step 0.1), which suggested that the combined Hedges'g (0.714; 95%CI: 0.645-0.783) with I^2: 0.00% ($P = 0.988$) corresponded to $0.7 < r < 0.8$; and (2) Direct calculation from Finucci *et al*[4], which resulted in $r = 0.642$ (Figure 7). QTc improvement after Tx remained unaffected by age ($P = 0.417$) and was negatively correlated with female ratio ($P = 0.002$), alcoholic etiology of cirrhosis ratio ($P < 0.001$), and age of the study ($P = 0.019$) (Figures 8A-D).

Pharmacological effects on QTc: The paradigm of β-blockers

The effect of β-blockers on QTc was investigated using data from three relevant studies. Patients with cirrhosis who were treated with β-blockers presented shorter QTc than those who were not (SMD = -0.540; 95%CI: -0.836 to -0.243; $P < 0.001$); I^2 was 0.0% (95%CI: 0.0%-92.1%; $P = 0.653$) (Supplementary Figure 3).

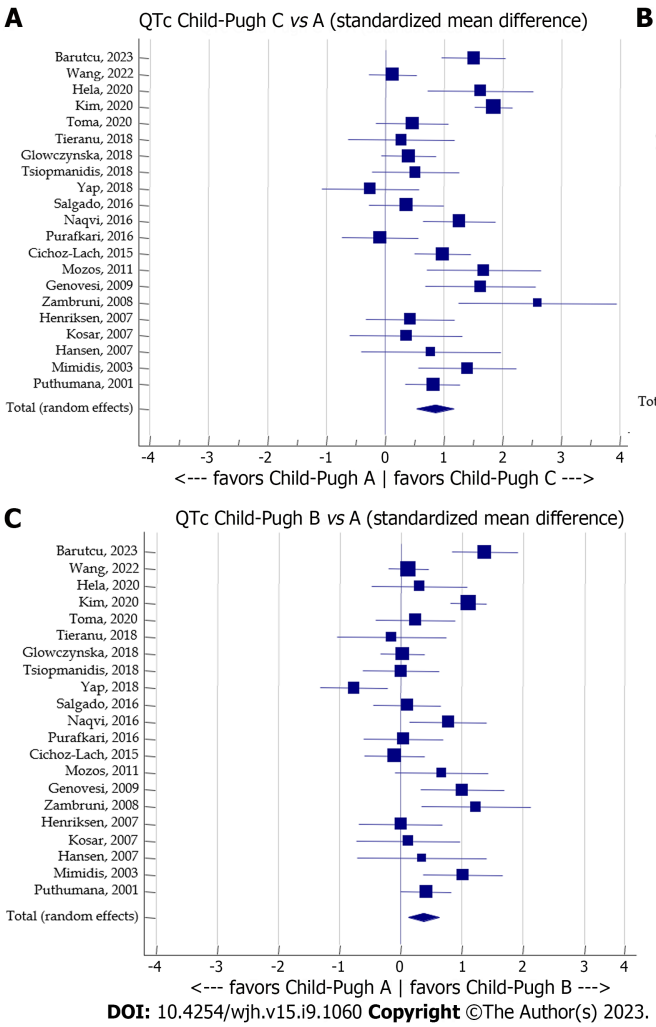

Figure 5 Meta-analysis forest plots concerning the effect of the Child-Pugh stage on corrected QT. A: Child-Pugh stage C *vs* A; B: Child-Pugh stage C *vs* B; C: Child-Pugh stage B *vs* A. QTc: Corrected QT.

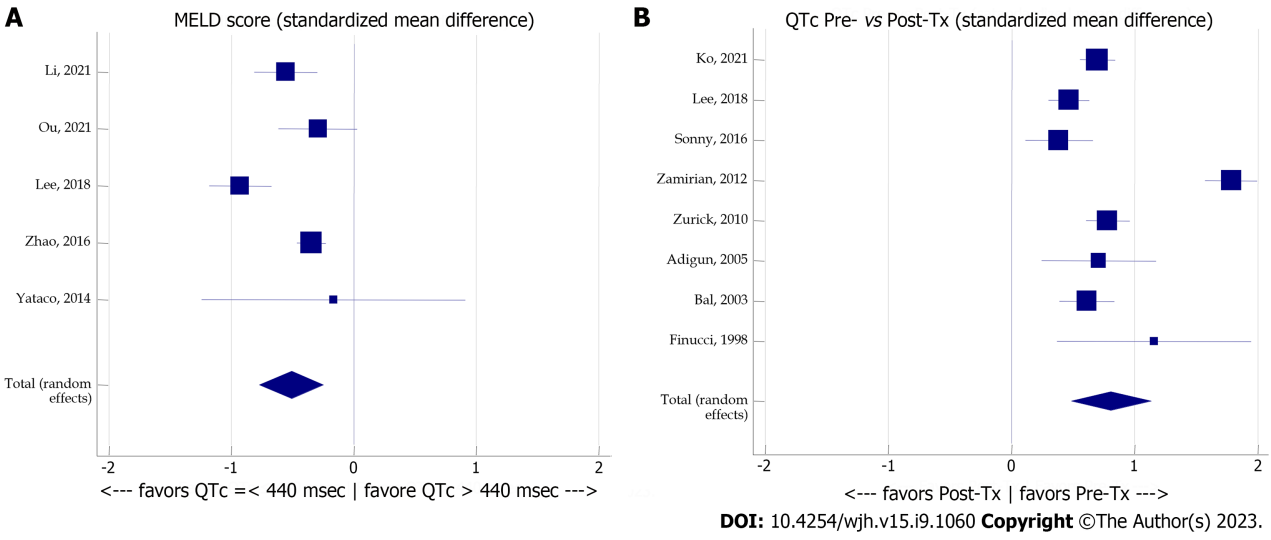

Figure 6 Meta-analysis forest plot concerning the effect of the model for end-stage liver disease score and liver transplantation on corrected QT. A: The effect of the model for end-stage liver disease score on corrected QT (QTc); B: The effect of liver transplantation on QTc. Tx: Transplantation; MELD: Model for end-stage liver disease; QTc: Corrected QT.

Acute gastrointestinal bleeding

QTc was prolonged during acute gastrointestinal bleeding, as deduced from two studies providing paired data (SMD = 1.800; 95%CI: 0.287-3.313; P = 0.020); I^2 was 96.7% (95%CI: 91.1%-98.8%; P < 0.001) (Supplementary Figure 4). Moreover, QTc was restored among survivors of an episode of gastrointestinal bleeding (SMD = 0.183; 95%CI: -0.051 to 0.417; P = 0.124); I^2 was 0.0% (95%CI: 0.0%-0.0%; P = 0.770) (Supplementary Figure 5).

Other potential sources of QTc heterogeneity

Meta-regression over 54 studies providing complete data revealed no independent correlation of QTc with study type (prospective *vs* others; bSD = -0.089; P = 0.517), device used (electrocardiograph *vs* Holter; bSD = 0.164; P = 0.237), or year of publication (bSD = 0.218; P = 0.118).

Overall survival according to QTc

Patients with cirrhosis with QTc ≤ 440 ms (n = 46) when compared with those with QTc > 440 ms (n = 40) had a survival HR of 2.666 [95%CI: 1.131-6.284; P = 0.025; standard error (SE) = 0.4375][3]. Similarly, patients with cirrhosis with QTc ≤ 440 ms (n = 247) when compared with those with QTc > 440 ms (n = 162) had a survival HR of 1.727 (95%CI: 1.054-2.828; P = 0.030; SE = 0.2518)[26]. Lastly, patients with cirrhosis with QTc ≤ 440 ms (n = 55) when compared with those with QTc > 440 ms (n = 55) had a survival HR of 2.464 (95%CI: 1.407-4.313; P = 0.0016; SE = 0.2858)[27]. These data demonstrated that patients with cirrhosis with QTc ≤ 440 ms when compared with those with QTc > 440 ms had a survival HR of 2.228 (95%CI: 1.640-2.815; P < 0.001) with an I^2 of 63.1% (95%CI: 0.0%-89.5%; P = 0.067) (Figure 9A).

Risk of bias assessment

The funnel plot referring to QTc/440 ratio combined mean was symmetric (Figure 9B). Moreover, both Egger's and Begg's tests showed non-significance (P = 0.151 and P = 0.985, respectively). The risk of bias assessment with the aid of the NOS and evaluation of evidence certainty derived from GRADE assessment are provided in Tables 2 and 3, respectively. Of note, no correlation of QTc with NOS low, intermediate, and high risk (P = 0.772) was detected, even after adjustment for alcoholic etiology rate and MELD score (P_{adj} = 0.651).

DISCUSSION

The present work represents the first systematic review and meta-analysis of QTc interval in cirrhosis. We demonstrated that QTc is prolonged in patients with cirrhosis compared with the most commonly used upper normal limit for QT interval (440 ms). Moreover, we showed that QTc prolongation in cirrhosis is linked with overall survival and is more evident in severe forms of the disease, as described by Child-Pugh stage, as well as in cases where alcohol as the etiology factor prevails when compared with viral hepatitis B or C. Interestingly, the fact that QTc prolongation in cirrhosis is a potentially reversible electrocardiographic abnormality is reflected by the fact that is at least partly restored after liver Tx.

Evidence of high quality indicates that liver Tx exerts a large beneficial effect in QTc. In contrast with Adigun *et al*[21], this amelioration has been shown to be negatively associated with age, male sex, and alcohol as the etiology of cirrhosis. This phenomenon could be partly attributed to the redefinition of QTc-affecting drugs, such as β-blockers and diuretics [77]. Moreover, both restoration of hepatocellular function and remission of portal hypertension might be considered helpful[6,32,92]. However, as portal decompression following transjugular intrahepatic portosystemic shunt increases QTc, the beneficial effect of liver Tx reflects only the amelioration of liver function[3,6,90]. Therefore, this compensatory mechanism might be compromised in patients with cirrhosis of alcohol etiology in cases that alcohol consumption persists. Moreover, diastolic dysfunction reflecting cirrhotic cardiomyopathy persists after liver Tx[77]. Patients with persistent QTc prolongation after liver Tx exhibit a worse prognosis[39].

High certainty of evidence has been also demonstrated that QTc prolongation in cirrhosis is more pronounced in severe forms of the disease, revealing a dose-response gradient effect of Child-Pugh score on QTc. It has been shown that patients with cirrhosis with QTc > 440 ms had higher MELD scores when compared with patients with QTc ≤ 440 ms. The correlation between the severity of cirrhosis and QTc prolongation might reflect the key role that aggravating hyperdynamic circulation leading to cirrhotic cardiomyopathy plays in the pathophysiology of the disease as well as the electrolyte imbalance superimposed by diuretic administration[80].

We have also concluded that alcohol, compared to the viral etiology of cirrhosis, leads to comparable QTc prolongation. This finding is in contrast with the fact that patients with cirrhosis related to alcoholic liver disease have been reported to present a worse outcome than those with cirrhosis related to chronic hepatitis C virus infection or non-alcoholic fatty liver disease[97]. Moreover, considering that alcohol causes cardiomyopathy *per se*, it could be argued that alcohol might well contribute to an inextricably intertwined entity involving alcoholic and cirrhotic cardiomyopathy in cases that it constitutes the unique or dominant cause of cirrhosis[62,64]. However, our result suggests that the contribution of alcohol in the pathophysiology of cirrhotic cardiomyopathy might be limited, if any.

Of note, other factors such as β-blockers, electrolyte imbalance due to diuretic treatment, and a recent episode of gastrointestinal bleeding might affect QTc. Similar to previous studies, we have demonstrated that β-blockers exert a negative effect on QTc[31,88,95]. Moreover, we showed that QTc is prolonged during acute gastrointestinal bleeding and is restored among survivors. This finding is also similar to recent studies[40,72]. However, the overall effect of treatments affecting QT, hospitalization for acute illness, and comorbidities on QTc prolongation in patients with cirrhosis is debatable if not negligible as suggested by the relevant sensitivity analysis carried out in the present study.

Table 2 Newcastle-Ottawa risk of bias assessment tool for all eligible studies

Ref.	Type	NOS selection	NOS comparability	NOS exposure[1] or outcome of interest[2]	Risk of bias
Wang *et al*[62], 2023	Retrospective study	**	*	***	Intermediate
Bilous *et al*[10], 2023	Prospective study	**	*	***	Intermediate
Barutcu *et al*[37], 2023	Retrospective study	***	**	***	Low
Lu *et al*[46], 2022	Retrospective study	***	*	***	Low
Wang *et al*[63], 2022	Retrospective study	**	**	***	Low
Li *et al*[27], 2021	Prospective study	****	**	***	Low
Ou *et al*[40], 2021	Retrospective study	****	*	***	Low
Ko *et al*[25], 2021	Retrospective study	****	**	***	Low
Héla *et al*[36], 2020	Prospective study	**	**	***	Low
Abrahamovych *et al*[64], 2020	Retrospective study	***	*	***	Low
Ibrahim *et al*[65], 2020	Prospective study	****	*	***	Low
Hussain *et al*[66], 2020	Prospective study	***	*	***	Low
Kim *et al*[35], 2020	Retrospective study	***	**	***	Low
Toma *et al*[67], 2020	Prospective study	***	**	***	Low
Bhardwaj *et al*[68], 2020	Prospective study	***	*	***	Low
Gaafar *et al*[69], 2019	Prospective study	***	*	***	Low
Kazankov *et al*[28], 2019	Retrospective study	****	*	***	Low
Moaref *et al*[70], 2019	Prospective study	***	*	***	Low
Santeusanio *et al*[71], 2019	Retrospective study	****	*	***	Low
Biselli *et al*[72], 2019	Retrospective study	****	*	**	Low
Tieranu *et al*[45], 2018	Prospective study	***	**	***	Low
Lee *et al*[39], 2018	Retrospective study	****	**	***	Low
Hajiaghamohammadi *et al*[73], 2018	Prospective study	***	*	**	Intermediate
Główczyńska *et al*[44], 2018	Retrospective study	***	**	***	Low
Tahata *et al*[74], 2018	Prospective study	****	*	***	Low
Tsiompanidis *et al*[75], 2018	Prospective study	***	**	***	Low
Yap *et al*[43], 2018	Retrospective study	**	**	***	Low
Kim *et al*[76], 2017	Retrospective study	***	*	**	Intermediate
Rimbaş *et al*[18], 2018	Prospective study	****	*	***	Low
Salgado *et al*[42], 2016	Prospective study	****	**	***	Low
Naqvi *et al*[34], 2016	Prospective study	***	**	***	Low

Zhao *et al*[38], 2016	Retrospective study	***	*	***	Low
Sonny *et al*[77], 2016	Retrospective study	***	**	***	Low
Barbosa *et al*[17], 2016	Case-control study	***	*	***	Low
Carvalheiro *et al*[78], 2016	Retrospective study	***	*	***	Low
Pourafkari *et al*[79], 2016	Retrospective study	***	**	***	Low
Barakat *et al*[80], 2015	Prospective study	**	*	***	Intermediate
Voiosu *et al*[81], 2015	Prospective study	***	*	***	Low
Cichoż-Lach *et al*[82], 2015	Retrospective study	**	**	***	Low
Peter *et al*[83], 2014	Prospective study	**	*	***	Intermediate
Moaref *et al*[15], 2014	Prospective study	**	*	***	Intermediate
Josefsson *et al*[84], 2014	Retrospective study	***	*	***	Low
Karagiannakis *et al*[14], 2014	Prospective study	***	*	***	Low
Yataco *et al*[41], 2014	Retrospective study	***	**	***	Low
Bhatti *et al*[85], 2014	Case-control study	**	*	***	Intermediate
Møller *et al*[86], 2012	Prospective study	***	*	***	Low
Trevisani *et al*[87], 2012	Retrospective study	****	*	***	Low
Zamirian *et al*[24], 2012	Prospective study	**	*	***	Intermediate
Kim *et al*[88], 2011	Prospective study	****	*	***	Low
Shin *et al*[89], 2011	Prospective study	***	*	***	Low
Mozos *et al*[33], 2011	Prospective study	***	**	***	Low
Vuppalanchi *et al*[90], 2011	Prospective study	**	*	***	Intermediate
Møller *et al*[91], 2010	Prospective study	***	*	***	Low
Zurick *et al*[23], 2010	Retrospective study	****	**	***	Low
Lossnitzer *et al*[13], 2010	Prospective study	***	*	***	Low
Genovesi *et al*[32], 2009	Prospective study	****	**	***	Low
Zambruni *et al*[31], 2008	Prospective study	****	**	**	Low
Henriksen *et al*[92], 2007	Prospective study	****	**	***	Low
Kosar *et al*[93], 2007	Retrospective study	****	**	***	Low
Hansen *et al*[12], 2007	Prospective study	**	**	***	Low
Zuberi *et al*[94], 2007	Case-control study	***	*	**	Intermediate
Zambruni *et al*[47], 2007	Prospective study	****	*	***	Low
Ytting *et al*[7], 2005	Prospective study	***	*	***	Low
Adigun *et al*[21], 2005	Prospective study	***	**	***	Low
Henriksen *et al*[95], 2004	Prospective study	***	*	***	Low
Bal and Thuluvath[26], 2003	Retrospective study	****	**	***	Low
Trevisani *et al*[6], 2003	Prospective study	***	*	***	Low
Mimidis *et al*[30], 2005	Retrospective	***	**	***	Low

	study				
Henriksen *et al*[11], 2002	Prospective study	***	*	***	Low
Puthumana *et al*[29], 2001	Retrospective study	***	**	***	Low
Quera *et al*[96], 2000	Retrospective study	***	*	**	Intermediate
Bernardi *et al*[3], 1998	Prospective study	****	**	***	Low
Finucci *et al*[4], 1998	Prospective study	****	**	***	Low

[1]For case-control studies.
[2]For cross-sectional studies.
NOS: Newcastle-Ottawa scale.

Table 3 GRADE assessment of evidence certainty (quality) for every endpoint

Endpoint	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias	Effect size	Quality
Cirrhosis effect (patients *vs* controls) on QTc	No important risk of bias	No important imprecision	No important inconsistency	No important indirectness	No important publication bias	Very large	Very high
QTc prolongation in cirrhosis (QTc *vs* 440 ms)	No important risk of bias	No important imprecision	No important inconsistency	No important indirectness	No important publication bias	Very large	Very high
Sex effect on QTc in cirrhosis	No important risk of bias	No important imprecision	Serious inconsistency	No important indirectness	No important publication bias	Trivial	Very low
Etiology of cirrhosis (alcohol *vs* viral) effect on QTc	No important risk of bias	No important imprecision	Serious inconsistency	No important indirectness	No important publication bias	Trivial	Very low
Child-Pugh stage (C *vs* B *vs* A) effect on QTc	No important risk of bias	No important imprecision	No important inconsistency	No important indirectness	No important publication bias	Medium with dose-response gradient	High
MELD score effect on QTc prolongation	No important risk of bias	No important imprecision	No important inconsistency	No important indirectness	No important publication bias	Medium	Low
β-blockers effect on QTc	No important risk of bias	No important imprecision	No important inconsistency	No important indirectness	No important publication bias	Medium	Low
Acute gastrointestinal bleeding effect on QTc	No important risk of bias	No important imprecision	Serious inconsistency	No important indirectness	No important publication bias	Very large	High
Liver transplantation effect on QTc	No important risk of bias	No important imprecision	No important inconsistency	No important indirectness	No important publication bias	Large	High
QTc prolongation effect on overall survival in cirrhosis	No important risk of bias	No important imprecision	No important inconsistency	No important indirectness	No important publication bias	Medium	Low

MELD: Model for end-stage liver disease; QTc: Corrected QT.

In line with Adigun *et al*[21], we found no essential effect of sex or age on QTc of patients with cirrhosis. However, sex-dependent QTc prespecified upper normal limits are often adopted in the overall relevant literature, as demonstrated in the present meta-analysis and Figure 3. The QTc prolongation ratio recorded in studies that do not share a common QTc upper normal limit for both males and females might be erroneous. According to our findings, using sex-specific or age-specific QTc upper normal values in this group of patients is not justified.

It is widely debated which upper normal limit should be used for QTc in patients with cirrhosis. In contrast with what is considered as QTc upper normal limit for patients without cirrhosis, namely < 430 ms for males and < 450 ms for females, 440 ms was adopted as the upper normal limit for QTc for both male and female patients with cirrhosis by the majority of the studies included (38/60; 63.3%; Figure 3)[98,99]. This choice was further supported by our result that patients with cirrhosis with QTc ≤ 440 ms, when compared with those with QTc > 440 ms, have at least twice the probability of surviving, thus conveying a clear-cut clinical meaning. The evidence above suggests that QTc ≤ 440 ms can be introduced as a surrogate prognostic marker for prolonged overall survival in cirrhosis.

Most studies adopted the Bazett formula ($QT_{Bazett} = QT/RR^{1/2}$), while the second most common formula was Fridericia ($QT_{Fridericia} = QT/RR^{1/3}$). In cases where the heart rate was 60-100 beats/min, $QT_{Fridericia}$ can be safely converted to QT_{Bazett} using the formula $QT_{Bazett} = QT_{Fridericia}/RR^{-1/6}$, given that QT_{Bazett} and $QT_{Fridericia}$ produce comparable QT corrections under these circumstances[100]. There is still much debate regarding the procedure that should be selected for the correction of

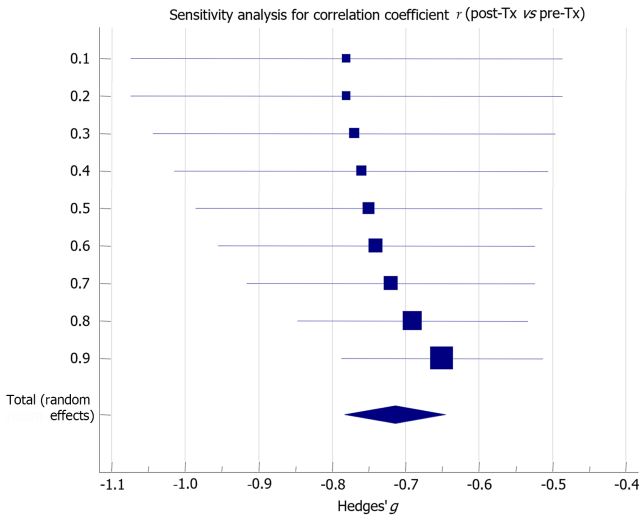

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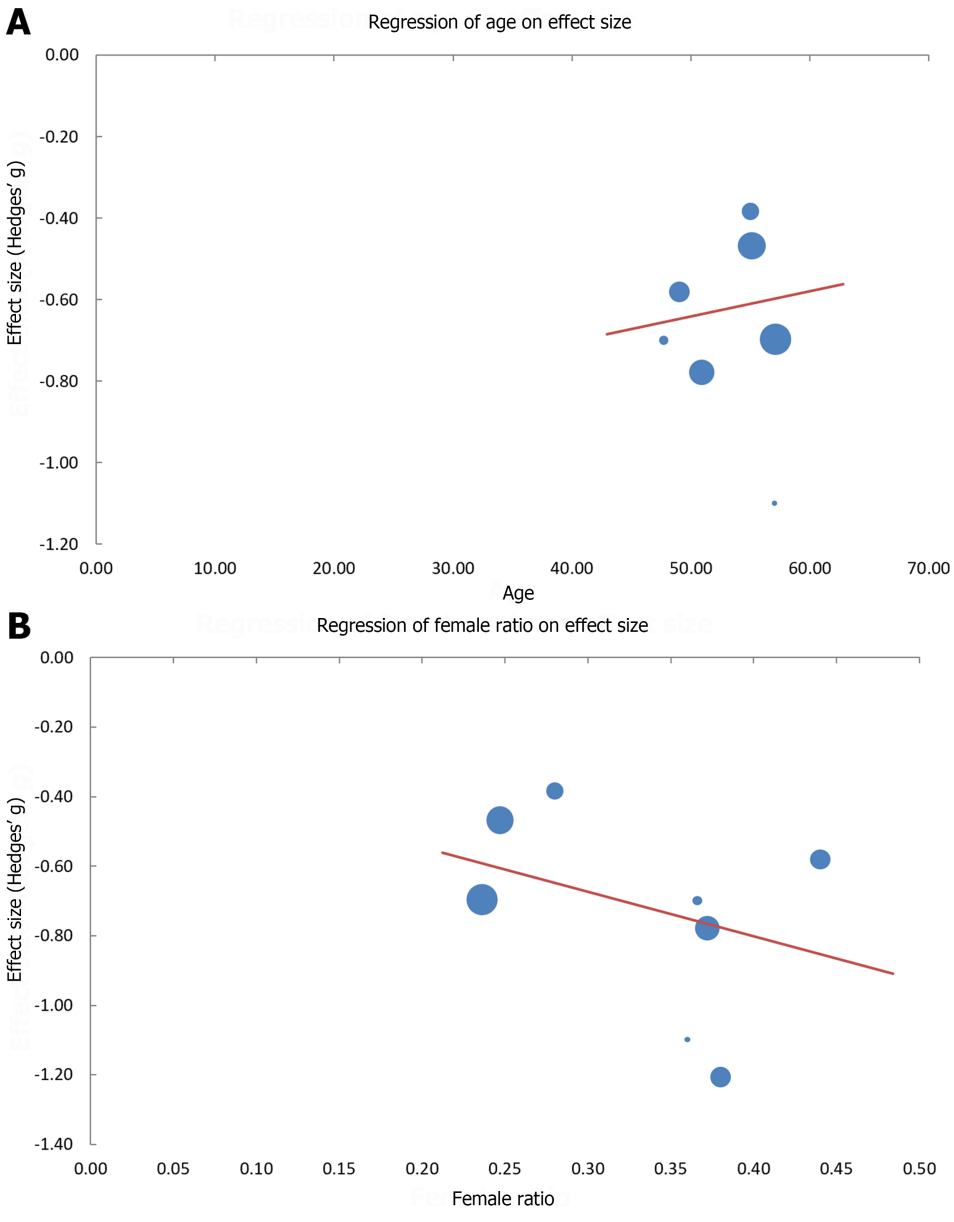
Figure 7 Sensitivity analysis forest plot concerning the estimation of the correlation coefficient between post-transplantation and pre-transplantation corrected QT values. Tx: Transplantation.



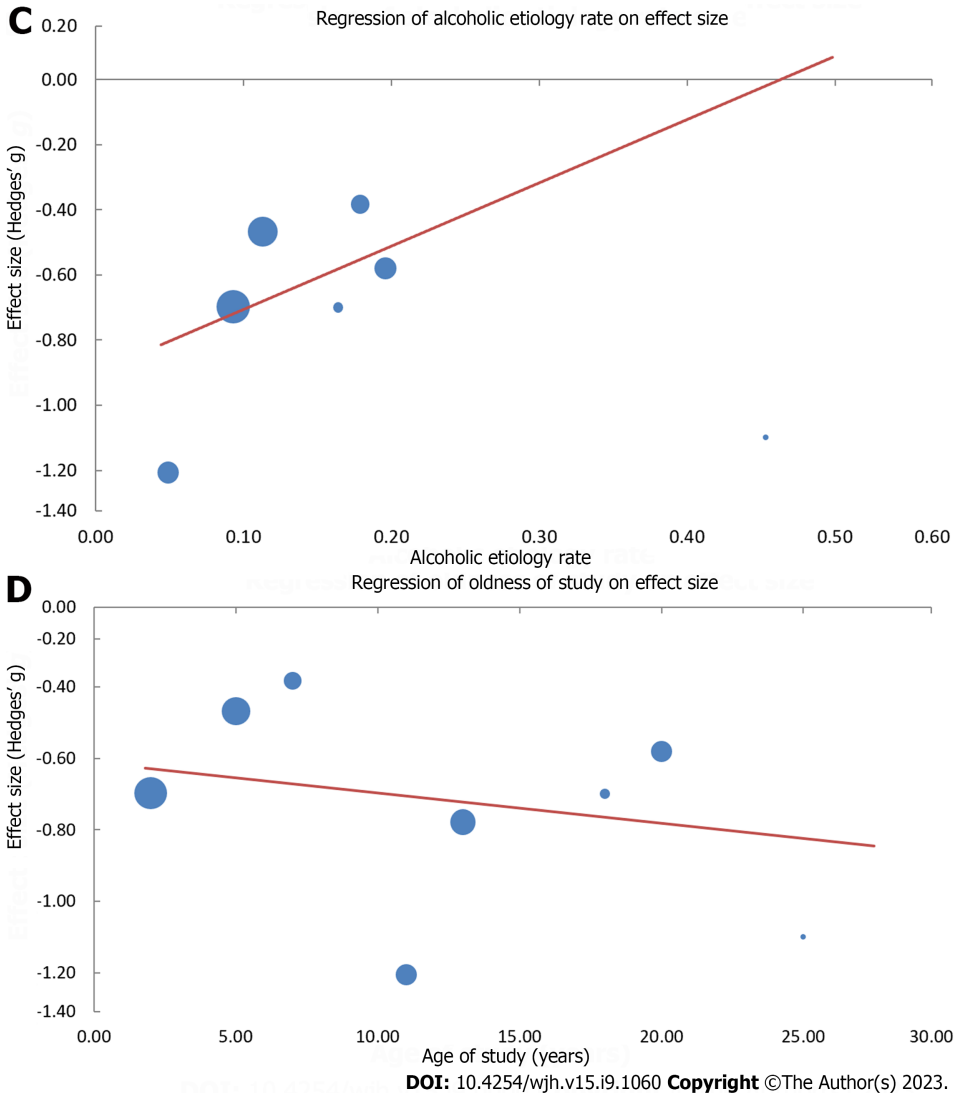


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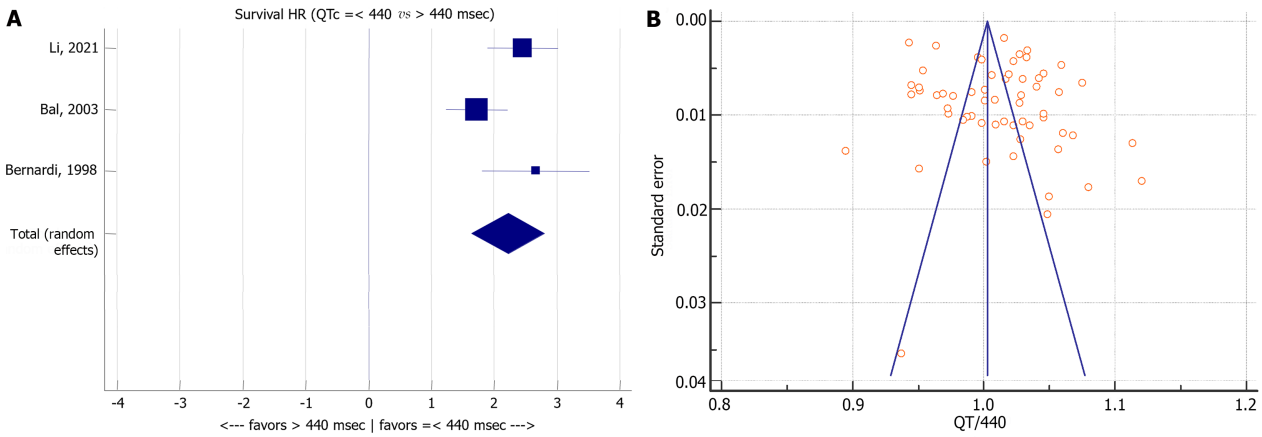
Figure 8 Plot points and regression lines on effect size, namely Hedges' *g*, reflecting correlations of pre-transplantation *vs* post-transplantation corrected QT. A: Age [H_g = -0.95 + 0.01 (yr); *P* = 0.417]; B: Female ratio [H_g = -0.29 - 1.28 (female ratio); *P* < 0.001]; C: Alcoholic etiology rate [H_g = -0.90 - 1.95 (alcoholic etiology rate); *P* < 0.001]; D: Age of study [H_g = -0.61 - 0.01 (age of study); *P* = 0.019]. H_g refers to Hedges'g.

QT in patients with cirrhosis, as there is evidence that they may lead to different clinical conclusions[31]. However, QT_{Bazett} was selected as the formula of choice in most of the included studies (68/73; 93.2%). Therefore, all current evidence derived from combining relevant effect sizes and summarized in Table 3 was based on QT_{Bazett}. Hence, authors should consider using the QT_{Bazett} as an at least additional formula to correct QT.

Interestingly, QTc length was not correlated with study type, year of publication, or even device used (electrocardiograph or Holter). This finding underlies that since no confounding parameters have been detected, the quality of evidence concerning QTc length remains very high, having been upgraded by two levels due to the very high relevant effect size.

Limitations

Apart from the apparent strengths regarding the quantitative and qualitative assessment of endpoints, the present study also had some limitations. First, the literature review was conducted by only two authors; while no different coauthor was available to resolve any discrepancies, the most experienced author (Mimidis K) undertook the latter task. Second, high heterogeneity was detected, which was not attributed to any specified potential confounder, such as publication bias, NOS scoring, study type, device used, year of publication, hospitalization for acute illness, comorbidities, and treatments affecting QT except β-blockers. Third, the effect of drugs on QTc could not be explicitly determined as detailed information concerning the use of medications, other than β-blockers, affecting QTc (including diuretics, anti-rejection regimens such as tacrolimus, antibiotics, antipsychotics, antidepressants, antiemetics, analgesics, antihistamines, and the direct antiviral agents lepidasvir and sofosbuvir) are lacking. Last, it might be claimed that performing meta-analysis with very few studies, as in the cases of the effect of β-blockers on QTc, acute gastrointestinal bleeding effect on QTc, and QTc prolongation effect on overall survival in cirrhosis, might be a limitation. However, when the results are not inconclusive, a quantitative meta-analysis is an acceptable approach[101].



DOI: 10.4254/wjh.v15.i9.1060

Figure 9 Meta-analysis forest plot concerning overall survival of patients with cirrhosis relating to corrected QT and corrected QT to upper normal limit (440 ms) ratio in patients with cirrhosis. A: Overall survival of patients with cirrhosis relating to corrected QT (QTc); B: QTc to upper normal limit (440 ms) ratio in patients with cirrhosis. QTc: Corrected QT; HR: Hazard ratio.

CONCLUSION

QTc is prolonged in cirrhosis independent of sex, age, and etiology. QTc is correlated with severity and is affected by β-blockers and acute gastrointestinal bleeding. QTc is improved after liver Tx.

ARTICLE HIGHLIGHTS

Research background

The effects of sex, age, severity, and etiology, as well as the role of treatment, acute illness, and liver transplantation (Tx) are largely unknown regarding corrected QT (QTc) in cirrhosis.

Research motivation

It is unknown whether QTc is prolonged in patients with cirrhosis and whether QTc is affected by factors such as sex, age, severity, etiology, regimens, acute illness, and liver Tx.

Research objectives

To investigate QTc clinical usefulness in cirrhosis.

Research methods

Seventy-three studies were considered eligible, as identified by application of the search protocol "{[QTc] OR [QT interval] OR [QT-interval] OR [Q-T syndrome]} AND {[cirrhosis] OR [Child-Pugh] OR [MELD]}" in PubMed, EMBASE, and Google Scholar databases.

Research results

QTc was prolonged in patients with cirrhosis independent of sex and age (444.8 ± 4.4 ms). QTc correlated with Child-Pugh stage and model for end-stage liver disease score. QTc improved after liver Tx.

Research conclusions

QT prolongation in cirrhosis is independent of sex and age, is aggravated in severe cases, and benefited by liver Tx.

Research perspectives

QTc interval could be further evaluated as a tool in the assessment of liver cirrhosis by clinicians.

FOOTNOTES

Author contributions: Papadopoulos VP contributed to design of the study; Papadopoulos VP and Mimidis K contributed to conception of the study, acquisition, analysis and interpretation of the data, and drafting of the manuscript; and all authors gave final approval of the manuscript.

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REFERENCES

1 **Wehr M**, Hess J, Noll B, Bode JC. [Cardiac findings in alcoholic liver disease]. *Med Klin (Munich)* 1990; **85**: 629-636, 681 [PMID: 2266911]
2 **Day CP**, James OF, Butler TJ, Campbell RW. QT prolongation and sudden cardiac death in patients with alcoholic liver disease. *Lancet* 1993; **341**: 1423-1428 [PMID: 8099138 DOI: 10.1016/0140-6736(93)90879-l]
3 **Bernardi M**, Calandra S, Colantoni A, Trevisani F, Raimondo ML, Sica G, Schepis F, Mandini M, Simoni P, Contin M, Raimondo G. Q-T interval prolongation in cirrhosis: prevalence, relationship with severity, and etiology of the disease and possible pathogenetic factors. *Hepatology* 1998; **27**: 28-34 [PMID: 9425913 DOI: 10.1002/hep.510270106]
4 **Finucci G**, Lunardi F, Sacerdoti D, Volpin R, Bortoluzzi A, Bombonato G, Angeli P, Gatta A. Q-T interval prolongation in liver cirrhosis. Reversibility after orthotopic liver transplantation. *Jpn Heart J* 1998; **39**: 321-329 [PMID: 9711183 DOI: 10.1536/ihj.39.321]
5 **Kempler P**, Szalay F, Váradi A, Keresztes K, Kádár E, Tánczos E, Petrik J. Prolongation of the QTc-interval reflects the severity of autonomic neuropathy in primary biliary cirrhosis and in other non-alcoholic liver diseases. *Z Gastroenterol* 1993; **31** Suppl 2: 96-98 [PMID: 7483730]
6 **Trevisani F**, Merli M, Savelli F, Valeriano V, Zambruni A, Riggio O, Caraceni P, Domenicali M, Bernardi M. QT interval in patients with non-cirrhotic portal hypertension and in cirrhotic patients treated with transjugular intrahepatic porto-systemic shunt. *J Hepatol* 2003; **38**: 461-467 [PMID: 12663238 DOI: 10.1016/s0168-8278(03)00057-6]
7 **Ytting H**, Henriksen JH, Fuglsang S, Bendtsen F, Møller S. Prolonged Q-T(c) interval in mild portal hypertensive cirrhosis. *J Hepatol* 2005; **43**: 637-644 [PMID: 16083986 DOI: 10.1016/j.jhep.2005.04.015]
8 **Mozos I**. Arrhythmia risk in liver cirrhosis. *World J Hepatol* 2015; **7**: 662-672 [PMID: 25866603 DOI: 10.4254/wjh.v7.i4.662]
9 **Lehmann M**, Bruns T, Stallmach A. Risk factors for QT interval prolongation owing to acute gastrointestinal haemorrhage in patients with cirrhosis. *Liver Int* 2013; **33**: 321 [PMID: 23121501 DOI: 10.1111/liv.12010]
10 **Bilous Z**, Abrahamovych O, Abrahamovych M, Fayura O, Fedets A. Characteristics of the autonomic nervous system state, assessed by the heart rate variability study in cirrhotic patients with syntropic cardiomyopathy and its features depending on the qt interval duration. *Georgian Med News* 2023; 78-82 [PMID: 36864797]
11 **Henriksen JH**, Fuglsang S, Bendtsen F, Christensen E, Møller S. Dyssynchronous electrical and mechanical systole in patients with cirrhosis. *J Hepatol* 2002; **36**: 513-520 [PMID: 11943423 DOI: 10.1016/s0168-8278(02)00010-7]
12 **Hansen S**, Møller S, Bendtsen F, Jensen G, Henriksen JH. Diurnal variation and dispersion in QT interval in cirrhosis: relation to haemodynamic changes. *J Hepatol* 2007; **47**: 373-380 [PMID: 17459513 DOI: 10.1016/j.jhep.2007.03.013]
13 **Lossnitzer D**, Steen H, Zahn A, Lehrke S, Weiss C, Weiss KH, Giannitsis E, Stremmel W, Sauer P, Katus HA, Gotthardt DN. Myocardial late gadolinium enhancement cardiovascular magnetic resonance in patients with cirrhosis. *J Cardiovasc Magn Reson* 2010; **12**: 47 [PMID: 20704762 DOI: 10.1186/1532-429X-12-47]
14 **Karagiannakis DS**, Vlachogiannakos J, Anastasiadis G, Vafiadis-Zouboulis I, Ladas SD. Diastolic cardiac dysfunction is a predictor of dismal prognosis in patients with liver cirrhosis. *Hepatol Int* 2014; **8**: 588-594 [PMID: 26202764 DOI: 10.1007/s12072-014-9544-6]
15 **Moaref A**, Zamirian M, Yazdani M, Salehi O, Sayadi M, Aghasadeghi K. The Correlation between Echocardiographic Findings and QT Interval in Cirrhotic Patients. *Int Cardiovasc Res J* 2014; **8**: 39-43 [PMID: 24936479]
16 **Ruiz-del-Árbol L**, Serradilla R. Cirrhotic cardiomyopathy. *World J Gastroenterol* 2015; **21**: 11502-11521 [PMID: 26556983 DOI: 10.3748/wjg.v21.i41.11502]
17 **Barbosa M**, Guardado J, Marinho C, Rosa B, Quelhas I, Lourenço A, Cotter J. Cirrhotic cardiomyopathy: Isn't stress evaluation always required for the diagnosis? *World J Hepatol* 2016; **8**: 200-206 [PMID: 26839643 DOI: 10.4254/wjh.v8.i3.200]
18 **Rimbaş RC**, Baldea SM, Guerra RDGA, Visoiu SI, Rimbaş M, Pop CS, Vinereanu D. New Definition Criteria of Myocardial Dysfunction in Patients with Liver Cirrhosis: A Speckle Tracking and Tissue Doppler Imaging Study. *Ultrasound Med Biol* 2018; **44**: 562-574 [PMID: 29306590 DOI: 10.1016/j.ultrasmedbio.2017.11.013]
19 **Carvalho MVH**, Kroll PC, Kroll RTM, Carvalho VN. Cirrhotic cardiomyopathy: the liver affects the heart. *Braz J Med Biol Res* 2019; **52**: e7809 [PMID: 30785477 DOI: 10.1590/1414-431X20187809]
20 **Koshy AN**, Gow PJ, Testro A, Teh AW, Ko J, Lim HS, Han HC, Weinberg L, VanWagner LB, Farouque O. Relationship between QT interval prolongation and structural abnormalities in cirrhotic cardiomyopathy: A change in the current paradigm. *Am J Transplant* 2021; **21**: 2240-2245 [PMID: 33453141 DOI: 10.1111/ajt.16500]
21 **Adigun AQ**, Pinto AG, Flockhart DA, Gorski JC, Li L, Hall SD, Chalasani N. Effect of cirrhosis and liver transplantation on the gender difference in QT interval. *Am J Cardiol* 2005; **95**: 691-694 [PMID: 15721125 DOI: 10.1016/j.amjcard.2004.10.054]
22 **Mohamed R**, Forsey PR, Davies MK, Neuberger JM. Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in

end-stage liver disease. *Hepatology* 1996; **23**: 1128-1134 [PMID: 8621144 DOI: 10.1002/hep.510230529]
23 **Zurick AO 3rd**, Spier BJ, Teelin TC, Lorenze KR, Alberte C, Zacks S, Lindstrom MJ, Pfau PR, Selzman K. Alterations in corrected QT interval following liver transplant in patients with end-stage liver disease. *Clin Cardiol* 2010; **33**: 672-677 [PMID: 21089111 DOI: 10.1002/clc.20801]
24 **Zamirian M**, Tavassoli M, Aghasadeghi K. Corrected QT interval and QT dispersion in cirrhotic patients before and after liver transplantation. *Arch Iran Med* 2012; **15**: 375-377 [PMID: 22642249]
25 **Ko J**, Koshy AN, Han HC, Weinberg L, Gow P, Testro A, Lim HS, Farouque O, Teh AW. Effect of liver transplantation on QT-interval prolongation and impact on mortality. *Int J Cardiol* 2021; **326**: 158-163 [PMID: 33186663 DOI: 10.1016/j.ijcard.2020.11.017]
26 **Bal JS**, Thuluvath PJ. Prolongation of QTc interval: relationship with etiology and severity of liver disease, mortality and liver transplantation. *Liver Int* 2003; **23**: 243-248 [PMID: 12895263 DOI: 10.1034/j.1600-0676.2003.00833.x]
27 **Li S**, Hao X, Liu S, Gong Y, Niu W, Tang Y. Prolonged QTc interval predicts long-term mortality in cirrhosis: a propensity score matching analysis. *Scand J Gastroenterol* 2021; **56**: 570-577 [PMID: 33792461 DOI: 10.1080/00365521.2021.1901307]
28 **Kazankov K**, Jensen HK, Watson H, Vilstrup H, Bernardi M, Jepsen P. QT interval corrected for heart rate is not associated with mortality in patients with cirrhosis and ascites. *Scand J Gastroenterol* 2019; **54**: 1376-1378 [PMID: 31609144 DOI: 10.1080/00365521.2019.1677767]
29 **Puthumana L**, Chaudhry V, Thuluvath PJ. Prolonged QTc interval and its relationship to autonomic cardiovascular reflexes in patients with cirrhosis. *J Hepatol* 2001; **35**: 733-738 [PMID: 11738100 DOI: 10.1016/s0168-8278(01)00217-3]
30 **Mimidis K**, Papadopoulos V, Thomopoulos K, Tziakas D, Ritis K, Dalla V, Kotsiou S, Nikolopoulou V, Hatseras D, Kartalis G. Prolongation of the QTc interval in patients with cirrhosis. *Ann Gastroenterol* 2003; **16**: 155-158
31 **Zambruni A**, Trevisani F, Di Micoli A, Savelli F, Berzigotti A, Bracci E, Caraceni P, Domenicali M, Felline P, Zoli M, Bernardi M. Effect of chronic beta-blockade on QT interval in patients with liver cirrhosis. *J Hepatol* 2008; **48**: 415-421 [PMID: 18194821 DOI: 10.1016/j.jhep.2007.11.012]
32 **Genovesi S**, Prata Pizzala DM, Pozzi M, Ratti L, Milanese M, Pieruzzi F, Vincenti A, Stella A, Mancia G, Stramba-Badiale M. QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium. *Clin Sci (Lond)* 2009; **116**: 851-859 [PMID: 19076059 DOI: 10.1042/CS20080325]
33 **Mozos I**, Costea C, Serban C, Susan L. Factors associated with a prolonged QT interval in liver cirrhosis patients. *J Electrocardiol* 2011; **44**: 105-108 [PMID: 21146831 DOI: 10.1016/j.jelectrocard.2010.10.034]
34 **Naqvi IH**, Mahmood K, Naeem M, Vashwani AS, Ziaullah S. The heart matters when the liver shatters! Cirrhotic cardiomyopathy: frequency, comparison, and correlation with severity of disease. *Prz Gastroenterol* 2016; **11**: 247-256 [PMID: 28053679 DOI: 10.5114/pg.2016.57962]
35 **Kim HJ**, Kang MJ, Chung LY, Lee SH, Chung EJ, Jung WT, Hwang JY, Cho JH. Clinical usefulness of corrected QT interval as an index of the severity of liver cirrhosis. *Kor J Gastroenterol* 2020; **35**: 334-342
36 **Héla E**, Sofien K, Kamel L, Asma O, Dalila G, Sondos K, Jamel K. QT interval abnormalities and heart rate variability in patients with cirrhosis. *Arab J Gastroenterol* 2020; **21**: 246-252 [PMID: 33012676 DOI: 10.1016/j.ajg.2020.08.001]
37 **Barutcu S**, Inanc I, Sabanoglu C, Polat E. Predictive value of Tp-e interval, Tp-e/QT, and Tp-e/QTc for disease severity in patients with liver cirrhosis. *Eur Rev Med Pharmacol Sci* 2023; **27**: 1110-1120 [PMID: 36808359 DOI: 10.26355/eurrev_202302_31214]
38 **Zhao J**, Qi X, Hou F, Ning Z, Zhang X, Deng H, Peng Y, Li J, Wang X, Li H, Guo X. Prevalence, Risk Factors and In-hospital Outcomes of QTc Interval Prolongation in Liver Cirrhosis. *Am J Med Sci* 2016; **352**: 285-295 [PMID: 27650234 DOI: 10.1016/j.amjms.2016.06.012]
39 **Lee SH**, Park M, Park KM, Gwag HB, Park J, Kim J, Choi GS, Lee SK, Kim GS. Corrected QT interval on the electrocardiogram after liver transplantation: Surrogate marker of poor clinical outcomes? *PLoS One* 2018; **13**: e0206463 [PMID: 30365563 DOI: 10.1371/journal.pone.0206463]
40 **Ou M**, Tian Y, Zhuang G, Peng Y. QTc interval prolongation in liver cirrhosis with upper gastrointestinal bleeding. *Med Clin (Barc)* 2021; **156**: 68-75 [PMID: 33309043 DOI: 10.1016/j.medcli.2020.06.059]
41 **Yataco ML**, Difato T, Bargehr J, Rosser BG, Patel T, Trejo-Gutierrez JF, Pungpapong S, Taner CB, Aranda-Michel J. Reversible non-ischaemic cardiomyopathy and left ventricular dysfunction after liver transplantation: a single-centre experience. *Liver Int* 2014; **34**: e105-e110 [PMID: 24529030 DOI: 10.1111/liv.12501]
42 **Salgado AA**, Barbosa PRB, Ferreira AG, Reis CASS, Terra C. Prognostic Value of a New Marker of Ventricular Repolarization in Cirrhotic Patients. *Arq Bras Cardiol* 2016; **107**: 523-531 [PMID: 28558079 DOI: 10.5935/abc.20160181]
43 **Yap EML**, Supe MGS, Yu II. Cardiac Profile of Filipino Patients With Liver Cirrhosis: A 10-Year Study. *Cardiol Res* 2018; **9**: 358-363 [PMID: 30627286 DOI: 10.14740/cr804]
44 **Główczyńska R**, Galas M, Ołdakowska-Jedynak U, Peller M, Tomaniak M, Raszeja-Wyszomirska J, Milkiewicz P, Krawczyk M, Zieniewicz K, Opolski G. Pretransplant QT Interval: The Relationship with Severity and Etiology of Liver Disease and Prognostic Value After Liver Transplantation. *Ann Transplant* 2018; **23**: 622-630 [PMID: 30177675 DOI: 10.12659/AOT.908769]
45 **Țieranu E**, Donoiu I, Istrătoaie O, Găman AE, Țieranu LM, Gheonea DI, Ciurea T. Q-T Interval Prolongation in Patients with Liver Cirrhosis. *Curr Health Sci J* 2018; **44**: 274-279 [PMID: 30647948 DOI: 10.12865/CHSJ.44.03.11]
46 **Lu LH**, Lv XY, Wu QM, Dong Q, Wang Z, Zhang SJ, Fu L, Wang Q, Song YQ. Comparison of Electrocardiogram and QT Interval between Viral Hepatitis Cirrhosis and Alcoholic Cirrhosis. *Cardiol Res Pract* 2022; **2022**: 6934418 [PMID: 36304796 DOI: 10.1155/2022/6934418]
47 **Zambruni A**, Di Micoli A, Lubisco A, Domenicali M, Trevisani F, Bernardi M. QT interval correction in patients with cirrhosis. *J Cardiovasc Electrophysiol* 2007; **18**: 77-82 [PMID: 17229304 DOI: 10.1111/j.1540-8167.2006.00622.x]
48 **Page MJ**, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71 [PMID: 33782057 DOI: 10.1136/bmj.n71]
49 **Page MJ**, Shamseer L, Tricco AC. Registration of systematic reviews in PROSPERO: 30,000 records and counting. *Syst Rev* 2018; **7**: 32 [PMID: 29463298 DOI: 10.1186/s13643-018-0699-4]
50 **Brown D**. A Review of the PubMed PICO Tool: Using Evidence-Based Practice in Health Education. *Health Promot Pract* 2020; **21**: 496-498 [PMID: 31874567 DOI: 10.1177/1524839919893361]
51 **Stang A**. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; **25**: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]
52 **Guyatt G**, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J,

Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; **64**: 383-394 [PMID: 21195583 DOI: 10.1016/j.jclinepi.2010.04.026]

53 **Azuero A**. A note on the magnitude of hazard ratios. *Cancer* 2016; **122**: 1298-1299 [PMID: 26882217 DOI: 10.1002/cncr.29924]

54 **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188 [PMID: 3802833 DOI: 10.1016/0197-2456(86)90046-2]

55 **Wan X**, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; **14**: 135 [PMID: 25524443 DOI: 10.1186/1471-2288-14-135]

56 **Luo D**, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res* 2018; **27**: 1785-1805 [PMID: 27683581 DOI: 10.1177/0962280216669183]

57 **Shi J**, Luo D, Weng H, Zeng XT, Lin L, Chu H, Tong T. Optimally estimating the sample standard deviation from the five-number summary. *Res Synth Methods* 2020; **11**: 641-654 [PMID: 32562361 DOI: 10.1002/jrsm.1429]

58 **Hebert AE**, Kreaden US, Yankovsky A, Guo D, Li Y, Lee SH, Liu Y, Soito AB, Massachi S, Slee AE. Methodology to standardize heterogeneous statistical data presentations for combining time-to-event oncologic outcomes. *PLoS One* 2022; **17**: e0263661 [PMID: 35202406 DOI: 10.1371/journal.pone.0263661]

59 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]

60 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]

61 **Suurmond R**, van Rhee H, Hak T. Introduction, comparison, and validation of Meta-Essentials: A free and simple tool for meta-analysis. *Res Synth Methods* 2017; **8**: 537-553 [PMID: 28801932 DOI: 10.1002/jrsm.1260]

62 **Wang C**, Gao H, Liu W, Chen J, Guo Y, Zhao P. Alcoholic cardiomyopathy in patients with alcoholic liver cirrhosis: a study across 10 years. *Eur J Gastroenterol Hepatol* 2023; **35**: 600-603 [PMID: 36966758 DOI: 10.1097/MEG.0000000000002541]

63 **Wang Z**, Qian R, Wang Y, Mo L, Ju B, Hu N, Wang P, He L, Wang J. QTc interval prolongation in the patients with primary biliary cholangitis. *Ann Noninvasive Electrocardiol* 2022; **27**: e12925 [PMID: 34854522 DOI: 10.1111/anec.12925]

64 **Abrahamovych M**, Tolopko S, Farmaha M, Ferko M, Bilous Z. Criteria for diagnosis of cardiomyopathy in patients with alcoholic liver cirrhosis before the onset of heart damage clinical signs. *Georgian Med News* 2020; 81-85 [PMID: 32383707]

65 **Ibrahim MG**, Sharafeldin AA, Mousa NI, Mousa TK, El Missiri AM. Effect of direct-acting antivirals on corrected QT interval and cardiac functions in patients with chronic hepatitis C virus infection. *Egypt Heart J* 2020; **72**: 7 [PMID: 32030482 DOI: 10.1186/s43044-020-0042-y]

66 **Hussain KH**, Singh D, Nizamani S. Comparison of Heart Rate and QTc Interval in Patients of Cirrhosis of Liver with Non Cirrhotic Controls. *Ann Pak Inst Med Sci* 2020; **16** [DOI: 10.48036/apims.v16i1.365]

67 **Toma L**, Stanciu AM, Zgura A, Bacalbasa N, Diaconu C, Iliescu L. Electrocardiographic Changes in Liver Cirrhosis-Clues for Cirrhotic Cardiomyopathy. *Medicina (Kaunas)* 2020; **56** [PMID: 32050594 DOI: 10.3390/medicina56020068]

68 **Bhardwaj A**, Joshi S, Sharma R, Bhardwaj S, Agrawal R, Gupta N. QTc prolongation in patients of cirrhosis and its relation with disease severity: An observational study from a rural teaching hospital. *J Family Med Prim Care* 2020; **9**: 3020-3024 [PMID: 32984166 DOI: 10.4103/jfmpc.jfmpc_341_20]

69 **Gaafar AE**, Abd El-Aal A, Alboraie M, Hassan HM, ElTahan A, AbdelRahman Y, Wifi MN, Omran D, Mansour SA, Hassan WM, Ismail M, El Kassas M. Prevalence of prolonged QT interval in patients with HCV-related chronic liver disease. *Egypt Heart J* 2019; **71**: 15 [PMID: 31659581 DOI: 10.1186/s43044-019-0016-0]

70 **Moaref A**, Zamirian M, Mirzaei H, Attar A, Nasrollahi E, Bahramvand Y. Myocardial contractile dispersion: A new marker for the severity of cirrhosis? *J Cardiovasc Thorac Res* 2019; **11**: 147-151 [PMID: 31384410 DOI: 10.15171/jcvtr.2019.25]

71 **Santeusanio AD**, Dunsky KG, Pan S, Schiano TD. The Impact of Cirrhosis and Prescription Medications on QTc Interval Before and After Liver Transplantation. *J Pharm Pract* 2019; **32**: 48-53 [PMID: 29092657 DOI: 10.1177/0897190017737896]

72 **Biselli M**, Gramenzi A, Lenzi B, Dall'Agata M, Pierro ML, Perricone G, Tonon M, Bellettato L, D'Amico G, Angeli P, Boffelli S, Bonavita ME, Domenicali M, Caraceni P, Bernardi M, Trevisani F. Development and Validation of a Scoring System That Includes Corrected QT Interval for Risk Analysis of Patients With Cirrhosis and Gastrointestinal Bleeding. *Clin Gastroenterol Hepatol* 2019; **17**: 1388-1397.e1 [PMID: 30557740 DOI: 10.1016/j.cgh.2018.12.006]

73 **Hajiaghamohammadi AA**, Daee MM, Zargar A, Ahmadi-Gooraji S, Rahban A, Attaran F. Q-T interval prolongation in cirrhosis: Relationship and severity. *Caspian J Intern Med* 2018; **9**: 239-243 [PMID: 30197768 DOI: 10.22088/cjim.9.3.239]

74 **Tahata Y**, Sakamori R, Urabe A, Morishita N, Yamada R, Yakushijin T, Hiramatsu N, Doi Y, Kaneko A, Hagiwara H, Yamada Y, Hijioka T, Inada M, Tamura S, Imai Y, Furuta K, Kodama T, Hikita H, Tatsumi T, Takehara T. Liver Fibrosis Is Associated With Corrected QT Prolongation During Ledipasvir/Sofosbuvir Treatment for Patients With Chronic Hepatitis C. *Hepatol Commun* 2018; **2**: 884-892 [PMID: 30094400 DOI: 10.1002/hep4.1206]

75 **Tsiompanidis E**, Siakavellas SI, Tentolouris A, Eleftheriadou I, Chorepsima S, Manolakis A, Oikonomou K, Tentolouris N. Liver cirrhosis-effect on QT interval and cardiac autonomic nervous system activity. *World J Gastrointest Pathophysiol* 2018; **9**: 28-36 [PMID: 29487764 DOI: 10.4291/wjgp.v9.i1.28]

76 **Kim SM**, George B, Alcivar-Franco D, Campbell CL, Charnigo R, Delisle B, Hundley J, Darrat Y, Morales G, Elayi SC, Bailey AL. QT prolongation is associated with increased mortality in end stage liver disease. *World J Cardiol* 2017; **9**: 347-354 [PMID: 28515853 DOI: 10.4330/wjc.v9.i4.347]

77 **Sonny A**, Ibrahim A, Schuster A, Jaber WA, Cywinski JB. Impact and persistence of cirrhotic cardiomyopathy after liver transplantation. *Clin Transplant* 2016; **30**: 986-993 [PMID: 27292629 DOI: 10.1111/ctr.12778]

78 **Carvalheiro F**, Rodrigues C, Adrego T, Viana J, Vieira H, Seco C, Pereira L, Pinto F, Eufrásio A, Bento C, Furtado E. Diastolic Dysfunction in Liver Cirrhosis: Prognostic Predictor in Liver Transplantation? *Transplant Proc* 2016; **48**: 128-131 [PMID: 26915857 DOI: 10.1016/j.transproceed.2016.01.010]

79 **Pourafkari L**, Ghaffari S, Nazeri L, Lee JB, Masnadi-Shirazi K, Tajlil A, Nader ND. Electrocardiographic findings in hepatic cirrhosis and their association with the severity of disease. *Cor et Vasa* 2016 [DOI: 10.1016/j.crvasa.2016.01.010]

80 **Barakat AA**, Metwaly AA, Nasr FM, El-Ghannam M, El-Talkawy MD, Taleb HA. Impact of hyponatremia on frequency of complications in patients with decompensated liver cirrhosis. *Electron Physician* 2015; **7**: 1349-1358 [PMID: 26516441 DOI: 10.14661/1349]

81 **Voiosu AM**, Daha IC, Voiosu TA, Mateescu BR, Dan GA, Băicuş CR, Voiosu MR, Diculescu MM. Prevalence and impact on survival of

hepatopulmonary syndrome and cirrhotic cardiomyopathy in a cohort of cirrhotic patients. *Liver Int* 2015; **35**: 2547-2555 [PMID: 25974637 DOI: 10.1111/liv.12866]

82 **Cichoż-Lach H**, Tomaszewski M, Kowalik A, Lis E, Tomaszewski A, Lach T, Boczkowska S, Celiński K. QT Interval Prolongation and QRS Voltage Reduction in Patients with Liver Cirrhosis. *Adv Clin Exp Med* 2015; **24**: 615-622 [PMID: 26469105 DOI: 10.17219/acem/28681]

83 **Peter G**, George PC, Villyoth MP, Sivaraman S, Hamza RE, Bahuleyan S, Srijith K, Haridas A, Abdul Sathar S, Sreesh S, Narayanan P, Vinayakumar KR. QT interval prolongation: a risk factor for development of hepatorenal syndrome in cirrhotic patients with acute variceal bleeding. *Trop Gastroenterol* 2014; **35**: 157-163 [PMID: 26012319 DOI: 10.7869/tg.203]

84 **Josefsson A**, Fu M, Björnsson E, Castedal M, Kalaitzakis E. Pre-transplant renal impairment predicts posttransplant cardiac events in patients with liver cirrhosis. *Transplantation* 2014; **98**: 107-114 [PMID: 24621533 DOI: 10.1097/01.TP.0000442781.31885.a2]

85 **Bhatti AB**, Ali F, Satti SA. Prolonged QTc Interval Is an Electrophysiological Hallmark of Cirrhotic Cardiomyopathy. *Open J Internal Med* 2014; **4**: 33-39 [DOI: 10.4236/ojim.2014.41006]

86 **Møller S**, Mortensen C, Bendtsen F, Jensen LT, Gøtze JP, Madsen JL. Cardiac sympathetic imaging with mIBG in cirrhosis and portal hypertension: relation to autonomic and cardiac function. *Am J Physiol Gastrointest Liver Physiol* 2012; **303**: G1228-G1235 [PMID: 23019196 DOI: 10.1152/ajpgi.00303.2012]

87 **Trevisani F**, Di Micoli A, Zambruni A, Biselli M, Santi V, Erroi V, Lenzi B, Caraceni P, Domenicali M, Cavazza M, Bernardi M. QT interval prolongation by acute gastrointestinal bleeding in patients with cirrhosis. *Liver Int* 2012; **32**: 1510-1515 [PMID: 22776742 DOI: 10.1111/j.1478-3231.2012.02847.x]

88 **Kim YK**, Hwang GS, Shin WJ, Bang JY, Cho SK, Han SM. Effect of propranolol on the relationship between QT interval and vagal modulation of heart rate variability in cirrhotic patients awaiting liver transplantation. *Transplant Proc* 2011; **43**: 1654-1659 [PMID: 21693252 DOI: 10.1016/j.transproceed.2011.02.017]

89 **Shin WJ**, Kim YK, Song JG, Kim SH, Choi SS, Song JH, Hwang GS. Alterations in QT interval in patients undergoing living donor liver transplantation. *Transplant Proc* 2011; **43**: 170-173 [PMID: 21335179 DOI: 10.1016/j.transproceed.2010.12.002]

90 **Vuppalanchi R**, Juluri R, Ghabril M, Kim S, Thong N, Gorski JC, Chalasani N, Hall SD. Drug-induced QT prolongation in cirrhotic patients with transjugular intrahepatic portosystemic shunt. *J Clin Gastroenterol* 2011; **45**: 638-642 [PMID: 20962670 DOI: 10.1097/MCG.0b013e3181f8c522]

91 **Møller S**, Iversen JS, Krag A, Bie P, Kjaer A, Bendtsen F. Reduced baroreflex sensitivity and pulmonary dysfunction in alcoholic cirrhosis: effect of hyperoxia. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**: G784-G790 [PMID: 20616307 DOI: 10.1152/ajpgi.00078.2010]

92 **Henriksen JH**, Gülberg V, Fuglsang S, Schifter S, Bendtsen F, Gerbes AL, Møller S. Q-T interval (QT(C)) in patients with cirrhosis: relation to vasoactive peptides and heart rate. *Scand J Clin Lab Invest* 2007; **67**: 643-653 [PMID: 17852825 DOI: 10.1080/00365510601182634]

93 **Kosar F**, Ates F, Sahin I, Karincaoglu M, Yildirim B. QT interval analysis in patients with chronic liver disease: a prospective study. *Angiology* 2007; **58**: 218-224 [PMID: 17495272 DOI: 10.1177/0003319707300368]

94 **Zuberi BF**, Ahmed S, Faisal N, Afsar S, Memon AR, Baloch I, Qadeer R. Comparison of heart rate and QTc duration in patients of cirrhosis of liver with non-cirrhotic controls. *J Coll Physicians Surg Pak* 2007; **17**: 69-71 [PMID: 17288849]

95 **Henriksen JH**, Bendtsen F, Hansen EF, Møller S. Acute non-selective beta-adrenergic blockade reduces prolonged frequency-adjusted Q-T interval (QTc) in patients with cirrhosis. *J Hepatol* 2004; **40**: 239-246 [PMID: 14739094 DOI: 10.1016/j.jhep.2003.10.026]

96 **Quera R**, Madrid AM, Ugalde H, Defilippi C. [Cisapride does not modify prolonged Q-T interval in patients with liver cirrhosis]. *Rev Med Chil* 2000; **128**: 847-852 [PMID: 11129545]

97 **Marot A**, Henrion J, Knebel JF, Moreno C, Deltenre P. Alcoholic liver disease confers a worse prognosis than HCV infection and non-alcoholic fatty liver disease among patients with cirrhosis: An observational study. *PLoS One* 2017; **12**: e0186715 [PMID: 29077714 DOI: 10.1371/journal.pone.0186715]

98 **Johnson JN**, Ackerman MJ. QTc: how long is too long? *Br J Sports Med* 2009; **43**: 657-662 [PMID: 19734499 DOI: 10.1136/bjsm.2008.054734]

99 **Lee W**, Vandenberk B, Raj SR, Lee SS. Prolonged QT Interval in Cirrhosis: Twisting Time? *Gut Liver* 2022; **16**: 849-860 [PMID: 35864808 DOI: 10.5009/gnl210537]

100 **Postema PG**, Wilde AA. The measurement of the QT interval. *Curr Cardiol Rev* 2014; **10**: 287-294 [PMID: 24827793 DOI: 10.2174/1573403X10666140514103612]

101 **Schulz A**, Schürmann C, Skipka G, Bender R. Performing Meta-analyses with Very Few Studies. *Methods Mol Biol* 2022; **2345**: 91-102 [PMID: 34550585 DOI: 10.1007/978-1-0716-1566-9_5]

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