ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2023 September 27; 15(9): 1013-1083

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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Editorial Board Member of *World Journal of Hepatology*, Paolo Muratori, MD, Full Professor of Internal Medicine, Department of Science for the Quality of Life, University of Bologna, Bologna 40138, Italy.
paolo.muratori3@unibo.it

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The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJH* as 2.4; IF without journal self cites: 2.3; 5-year IF: 3.0; Journal Citation Indicator: 0.47. The *WJH*'s CiteScore for 2022 is 3.6 and Scopus CiteScore rank 2022: Hepatology is 42/70.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Xiang Li*.

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Nikolaos Pyrsopoulos, Ke-Qin Hu, Koo Jeong Kang

EXECUTIVE ASSOCIATE EDITORS-IN-CHIEF

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PUBLICATION DATE
September 27, 2023

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World Journal of Hepatology

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World J Hepatol 2023 September 27; 15(9): 1013-1020

DOI: 10.4254/wjh.v15.i9.1013

ISSN 1948-5182 (online)

MINIREVIEWS

Noninvasive prognostic models, imaging, and elastography to predict clinical events in primary sclerosing cholangitis: A review

Mark W Russo

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Stojanovic B, Serbia; Xie Q, China

Received: April 7, 2023
Peer-review started: April 7, 2023
First decision: June 25, 2023
Revised: July 17, 2023
Accepted: August 23, 2023
Article in press: August 23, 2023
Published online: September 27, 2023

Mark W Russo, Division of Hepatology, Atrium Health Wake Forest, Charlotte, NC 28204, United States

Corresponding author: Mark W Russo, FAASLD, AGAF, FACG, MD, Professor, Divison of Hepatology, Atrium Health Wake Forest, 6th Floor MMP, 1025 Morehead Medical Dr, Charlotte, NC 28204, United States. mark.russo@atriumhealth.org

Abstract

Surrogate endpoints are needed to estimate clinical outcomes in primary sclerosing cholangitis (PSC). Serum alkaline phosphatase was among the first markers studied, but there is substantial variability in alkaline phosphatase levels during the natural history of PSC without intervention. The Mayo risk score incorporates noninvasive variables and has served as a surrogate endpoint for survival for more than two decades. Newer models have better test performance than the Mayo risk score, including the primary sclerosing risk estimate tool (PREsTo) model and UK-PSC score that estimate hepatic decompensation and transplant free survival, respectively. The c-statistics for transplant-free survival for the Mayo risk model and the long-term UK-PSC model are 0.68 and 0.85, respectively. The c-statistics for hepatic decompensation for the Mayo risk model and PREsTo model are 0.85 and 0.90, respectively. The Amsterdam-Oxford model included patients with large duct and small duct PSC and patients with PSC-autoimmune hepatitis overlap and had a c-statistic of 0.68 for transplant-free survival. Other noninvasive tests that warrant further validation include magnetic resonance imaging, elastography and the enhanced liver fibrosis score. Prognostic models, noninvasive tests or a combination of these surrogate endpoints may not only serve to be useful in clinical trials of investigational agents, but also serve to inform our patients about their prognosis.

Key Words: Cholestatic; Survival; Mortality; Predict; Cirrhosis; Decompensation

Core Tip: Several noninvasive prognostic models have been validated that improve upon serum alkaline phosphatase and the Mayo risk score or include subgroups of patients not validated by these tests. The UK-PSC score has superior test performance compared to the Mayo risk score for short and long term transplant free survival. The Primary sclerosing risk estimate tool (PREsTo) has excellent test performance for risk of hepatic decompensation. The Amsterdam-Oxford model includes patients with small duct primary sclerosing cholangitis (PSC) and PSC-autoimmune hepatitis overlap. Elastography and magnetic resonance imaging show promise as prognostic tools.

Citation: Russo MW. Noninvasive prognostic models, imaging, and elastography to predict clinical events in primary sclerosing cholangitis: A review. *World J Hepatol* 2023; 15(9): 1013-1020
URL: https://www.wjgnet.com/1948-5182/full/v15/i9/1013.htm
DOI: https://dx.doi.org/10.4254/wjh.v15.i9.1013

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease associated with diffuse inflammation of the biliary treat that may lead to cirrhosis, complications from portal hypertension and cholangiocarcinoma. The diagnosis is typically established on cholangiogram obtained during endoscopic retrograde cholangiography or magnetic resonance cholangiography and less commonly from findings on liver biopsy. The estimated prevalence of PSC varies by geographic location and ranges from 0.1-13.6 per 100000 with higher rates seen in Scandinavian countries and the United States[1]. The median transplant free survival is 21 years and there is no effective medical therapy that improves upon this outcome [2].

The etiology of PSC is not known but proposed mechanisms include dysregulation of the immune system, alterations in bile duct transporters that result in accumulation of toxic bile salts, gut microbiome interactions and immune mediated injury to the biliary epithelium, or environment triggers in genetically susceptible individuals[3].

There have been a number of drugs that have been evaluated for the treatment of PSC[4-6]. Because it would take years or even decades to evaluate the effect of a medication on liver related events on survival surrogate endpoints are needed. A consensus group suggested noninvasive surrogate endpoints are needed for clinical trials, which are preferred to more invasive surrogate endpoints such as liver biopsy or ERCP[7]. Serum alkaline phosphatase (ALP) and the Mayo model, which initially included liver histology, were among the first surrogate endpoints for PSC[8,9]. Since a prior review on this topic noninvasive prognostic models have been developed and validated with excellent test performance[10]. The most common clinical outcomes that surrogate endpoints have been associated with include liver transplant free survival, hepatic decompensation and cholangiocarcinoma. A review of the topic of noninvasive prognostic tests and models is timely because there are a number of molecules under development and noninvasive surrogate tests are recommended as endpoints in clinical trials[7].

MATERIALS AND METHODS

The focus of this invited review is to discuss noninvasive surrogate endpoints for patients with PSC and how they compare to ALP and Mayo Risk Score. Key words or search terms used to identify relevant articles published in English from January 1, 2000 to January 1, 2023 that were entered into PUBMED, OVID and EMBASE included "primary sclerosing cholangitis" and "biomarkers", "primary sclerosing cholangitis" and "prognostic score", "primary sclerosing cholangitis" and "model" and "prognosis", "primary sclerosing cholangitis" and "elastography". The references of articles were reviewed for additional relevant articles.

SERUM MARKERS

ALP and total bilirubin

A reduction or normalization of ALP has been associated with improved outcomes in patients with PSC. In a study of 86 patients with PSC, 38 (44%) achieved ALP normalization within 12 months of diagnosis[11]. Normalization of ALP was not associated with ursodeoxycholic acid (UDCA) therapy or therapeutic endoscopic retrograde cholangiography. Persistent ALP normalization was associated with a 79% lower risk of death, hepatobiliary neoplasia, or liver transplantation. In a separate study, patients with PSC who achieved an ALP less than 1.5 times the upper limit of normal had lower rate of a composite outcome (liver decompensation, liver transplantation, liver related deaths, cholangiocarcinoma) compared to those who did not have a reduction in ALP, 6% *vs* 38%, $P = 0.0002$[12]. Among 692 patients with PSC, an ALP > 1.3 × upper limit of normal (ULN) at 1 year of follow-up was associated with a 2-fold greater risk of liver transplant or PSC related death (death from end stage liver failure, cholangiocarcinoma or liver surgery)[13]. A reduction in ALP is associated with improved transplant free survival in patients with PSC with or without dominant strictures[14].

Among UDCA treated PSC patients who did and did not have ALP levels decrease by 40% or more after 1 year, 12 year survival was 90% and 47%, respectively, $P = 0.001$[15]. Patients in the placebo group had better survival if they had a 40% reduction or more in ALP after 1 year compared to those who did not have a decline in ALP. In a study that included patients who were and were not treated with UDCA no patient with persistently normal ALP reached a clinical endpoint (cholangiocarcinoma, liver transplantation or death) compared to 33% with persistent ALP abnormalities[16].

Patients with PSC have substantial variability in ALP levels over 5 years with 65% and 34% of patients achieving an ALP < 1.5 × ULN or normalizing ALP, respectively[17]. Despite variability in ALP levels, an ALP that declined to < 1.5 × ULN was independently associated with death, liver transplantation, hepatic decompensation or cholangiocarcinoma. However, others have shown that ALP reductions of 40% or more from baseline are seen in 15%-18% of patients with PSC at 2 years that are not associated with disease progression[18].

Total bilirubin

Total bilirubin is associated with lower survival in patients with PSC, but studies demonstrating this association have included patients with advanced disease, thus limiting its usefulness in patients with early stage PSC[19,20].

Enhanced liver fibrosis score and test

Enhanced liver fibrosis (ELF) score (R&D systems, Orion diagnostics, Espoo Finland) and ELF test (Siemens Medical Solutions Diagnostics Inc., Tarrytown, NY, United States) are derived from algorithms that include tissue inhibitor of metalloproteinase I, hyaluronic acid, and propeptide of type III procollagen. The association between transplant free survival and ELF score was derived and validated in 167 and 138 PSC patients, respectively. ELF score was independent of Mayo Risk Score and had a c-statistic of 0.82 for transplant free survival. A score of 10.6 or higher was associated with lower transplant free survival independent of Mayo Risk Score[21]. The ELF test was better than the ELF score at identifying the group at low risk for clinical endpoints. In a clinical trial that randomized patients with PSC to simtizumab or placebo, an ELF test ≥ 9.8 was associated with PSC-related progression events (ascites, spontaneous bacterial peritonitis, variceal hemorrhage, hepatic encephalopathy, ascending cholangitis, cholangiocarcinoma, hepatocellular carcinoma, liver transplantation, and death)[22]. Among those with an ELF test ≥ 9.8, 34% experienced a clinical event compared to 11% of those with scores below this threshold.

Among patients with PSC and cholangiocarcinoma, the ELF test was higher compared to those with PSC alone, 11.4 and 9.9, respectively $P < 0.001$[23]. In multivariable analysis an ELF test ≥ 9.8 was associated with a diagnosis of cholangiocarcinoma in patients with PSC (OR = 4.91, 95%CI: 1.19-20.21, $P = 0.021$).

NONINVASIVE PROGNOSTIC MODELS

Mayo risk score

The Mayo Risk Score was developed and validated in 405 patients and 124 patients, respectively with PSC from five centers[24]. The earlier Mayo Model for PSC required liver biopsy because histologic stage of PSC is a variable in the model[8,9]. The Mayo Risk Score includes age, total bilirubin, aspartate aminotransferase, variceal bleeding (yes/no), and albumin (Table 1). In the Mayo risk score study median follow up was 36 mo and the outcome was overall survival up to 4 years. Newer models that have been compared to the Mayo Risk Score will be discussed in further detail below.

Amsterdam-Oxford model

The Amsterdam-Oxford model was developed and validated among 956 patients with PSC from 44 Dutch hospitals or referral centers[25]. Large duct PSC was diagnosed in 91% of patients, 4% had PSC-autoimmune hepatitis overlap, 71% had inflammatory bowel disease, and 80% of the derivation cohort was taking UDCA. Median follow-up was 110 mo and the primary outcome was a composite outcome of liver transplant or PSC-related death (death from end-stage liver failure, death from liver surgery, death from cholangiocarcinoma or death from colorectal carcinoma).

The Amsterdam-Oxford model includes PSC subtype, age at diagnosis, albumin, platelets, aspartate aminotransferase, ALP, and total bilirubin (Table 2). The c-statistics for the primary outcome at 3 years of follow-up in the validation cohort were 0.66 with similar c-statistics at 1 and 2 years of follow-up (Figure 1).

A study from three centers in Italy, Belgium and The Netherlands evaluated the test performance of the Amsterdam-Oxford model and compared it to the Mayo Risk Score[26]. The cohort included 534 patients of which 3% had small duct PSC, 10% had PSC-autoimmune hepatitis overlap, 60% had inflammatory bowel disease and 92% were on UDCA therapy. The primary outcome was transplant free survival. The c-statistics for Amsterdam-Oxford model and Mayo Risk Score at 5 years of follow-up in the validation cohort were 0.76 and 0.79, respectively.

Primary sclerosing cholangitis risk estimate tool

Primary sclerosing cholangitis risk estimate tool (PREsTo) was developed and validated in 787 patients with PSC from centers in North America and Norway[27]. Patients with small duct PSC or PSC-autoimmune hepatitis overlap were excluded and approximately 70% of patients had inflammatory bowel disease. The number of patients on UDCA was not provided. Median follow-up was 6 and 4 years for the derivation and validation cohorts, respectively. The primary outcome was hepatic decompensation defined as variceal hemorrhage, hepatic encephalopathy, or ascites.

The authors employed artificial intelligence and used gradient boosting machines, a machine learning technique, to identify variables associated with hepatic decompensation. Variables included in the PREsTo model include total

Table 1 Noninvasive prognostic tests for primary sclerosing cholangitis

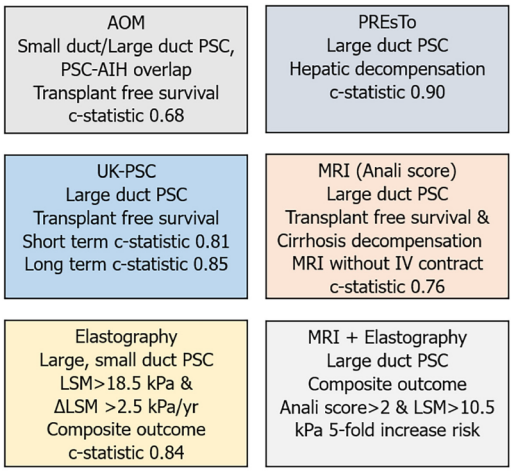
Serum markers	Models	Elastography	Imaging
Alkaline phosphatase; Total bilirubin; Enhanced liver fibrosis score	Mayo Risk Score; UK-PSC score; Amsterdam-Oxford Model; PREsTo score	Vibration controlled transient elastography; Magnetic resonance elastography	Magnetic resonance imaging-Anali score

PSC: Primary sclerosing cholangitis; PREsTo: Primary sclerosing risk estimate tool.

Table 2 Variables in noninvasive prognostic models for primary sclerosing cholangitis

	MRS	AOM	PREsTo	UK-PSC$_{ST}$	UK-PSC$_{LT}$
Age	√	√			
PSC subtype		√			√
Albumin	√	√	√	√	
ALP		√	√		√
AST	√		√		
Hemoglobin			√	√	
Platelets		√	√	√	√
Sodium			√		
Total bilirubin	√	√	√	√	√
Variceal bleed	√				√

AOM: Amsterdam-Oxford Model; ALP: Alkaline phosphatase; AST: Aspartate transaminase; MRS: Mayo Risk Score; PSC: Primary sclerosing cholangitis; PREsTo: Primary sclerosing risk estimate tool.



DOI: 10.4254/wjh.v15.i9.1013

Figure 1 Noninvasive prognostic models and test performance for primary sclerosing cholangitis. AOM: Amsterdam-Oxford Model; PREsTo: Primary sclerosing risk estimate tool; MRI: Magnetic resonance imaging; PSC: Primary sclerosing cholangitis; LSM: Liver stiffness measurements.

bilirubin, ALP, albumin, alanine aminotransferase, platelets, sodium, and hemoglobin (Table 1). Total bilirubin, albumin and ALP had the highest relative importance in the PREsTo model. In the validation cohort the c-statistic was 0.90 for PREsTo for 5-year risk of decompensation compared to c-statistics of 0.72, 0.85, and 0.65 for model for end stage liver disease score, Mayo Risk Score, and ALP < 1.5 × ULN, respectively.

UK-PSC score

The UK-PSC score was developed and validated in 1452 patients with PSC from 155 sites throughout the United Kingdom[28]. All patients had large duct PSC, 73% had inflammatory bowel disease, and 57% were on UDCA. Median follow-up ranged from 6-14.8 years in the validation and derivation cohorts. The primary outcome was transplant-free survival.

A short-term model for 2-year outcome and long-term model for 10-year outcomes were developed. The variables in the short-term UK-PSC score include total bilirubin, albumin, hemoglobin and platelet count (Table 2). The long-term model includes baseline and year 2 total bilirubin, platelet count, ALP, disease type (presence or absence of extrahepatic biliary disease) and history of variceal bleed (yes/no). In the validation cohort the c-statistics for short term UK-PSC model, Mayo Risk Score, model for end stage liver disease score were 0.81, 0.73, and 0.78, respectively. The c-statistics for long term UK-PSC model, Mayo Risk Score and aspartate aminotransferase platelet ratio index were 0.85, 0.69, and 0.70, respectively (Figure 1).

IMAGING

Magnetic resonance imaging

Features on magnetic resonance imaging (MRI) with cholangiography have been associated with outcomes in patients with PSC called the Anali score developed by Ana Ruiz and Lionel Arrive[29]. Based 289 MRI images from 64 patients with a median follow-up of 4 years a model for findings on MRI without and with contrast were developed to predict radiologic progression. The Anali score without gadolinium includes dilatation of intrahepatic bile ducts, dysmorphy, and portal hypertension while the score with gadolinium includes dysmorphy and parenchymal enhancement heterogeneity. Dysmorphy was defined as significant atrophy of either the right or left hepatic lobe and/or marked lobulations of the liver surface and/or increase in the caudate/right lobe ratio. The c-statistics for the Anali scores with and without gadolinium were 0.83 and 0.80, respectively (Figure 1)[29].

The MRI derived Anali score was validated in a study that included 338 patients with large duct PSC from France, Canada, Italy and the United Kingdom equally divided between a derivation and validation cohort[30]. The primary endpoint was transplant free survival or cirrhosis decompensation. The c-statistics for the primary outcome for the Anali score with and without gadolinium in the validation cohort were 0.73 and 0.76, respectively[30].

Transient elastography and magnetic resonance elastography

Liver stiffness measurements (LSM) obtained by vibration controlled transient elastography at baseline and during follow-up are associated with outcomes. A prospective study that included patients with large duct, small duct PSC (9%) or PSC-autoimmune hepatitis (3%) overlap reported adverse outcomes associated with baseline LSM and change in LSM [31]. Adverse outcomes were defined as a composite of death, liver transplantation, ascites, hepatic encephalopathy, gastrointestinal bleeding related to portal hypertension, cholangiocarcinoma or hepatocellular carcinoma. All patients were on UDCA and 68% had inflammatory bowel disease. The LSMs with highest accuracy for adverse outcomes were LSM > 18.5 kPa and change in LSM > 4 kPa/yr.

The group that developed PREsTo demonstrated an increase in magnetic resonance elastography (MRE) score is associated with hepatic decompensation (ascites, variceal hemorrhage or hepatic encephalopathy)[32]. In this study of 204 patients with PSC of which 82% had inflammatory bowel disease and 34% were on UDCA reported an increase of LSM > 0.34 kPa/yr had a c-statistic of 0.79 for hepatic decompensation. Combining a LSM > 4.32 kPa at baseline and an increase > 0.34 kPa/yr had a c-statistic of 0.93 for hepatic decompensation.

MRI and vibration controlled transient elastography

In a retrospective study that included 162 patients with PSC from 3 centers, Anali score without gadolinium and vibration controlled transient elastography (VCTE) were combined to risk stratify patients at risk for liver transplantation or cirrhosis decompensation[33]. Patients were categorized into three groups: Anali score ≤ 2 and LSM < 10.5 kPa, Anali score > 2 or LSM > 10.5 kPa, or Anali score > 3 and LSM score > 10.5 kPa. An Anali score > 2 and LSM > 10.5 kPa was associated with a 5-year risk of liver transplantation, death or cirrhosis decompensation of 38% compared to 8% for those with an Anali score ≤ 2 and LS ≤ 10.5 kPa, $P < 0.001$.

DISCUSSION

Despite the development and validation of several prognostic models and the evolution of imaging and elastography, ALP has persevered as a surrogate marker for disease progression in PSC. ALP or changes in ALP remain as an outcome in clinical trials of investigational agents for PSC[34-39]. The simplicity and availability of ALP make it an attractive biomarker in clinical practice. However, there is variability in ALP that occurs over time without any intervention, and it has inferior test performance compared to more recently validated prognostic models. Despite these limitations, ALP, it remains a variable in Amsterdam-Oxford model, PREsTo and UK-PSC$_{LT}$ models (Table 2). The ELF score has been associated with survival or cholangiocarcinoma but requires further validation. Furthermore, ELF is associated with added cost compared to noninvasive prognostic models where variables and lab data are usually already available.

The Mayo Risk Score has stood the test of time, but a criticism has been that the study cohort included a large number of patients with advanced PSC and the time span for the model is limited to 4 years. The PREsTo and UK-PSC scores provide estimates for outcomes at 5 and 10 years of follow-up. The test performance of UK-PSC and PREsTo models are better compared to the Mayo Risk Score.

Each of the models has its role in informing our patients with PSC about their prognosis (Figure 1). The UK-PSC model provides short-term and long-term estimates of transplant free survival. The PREsTo score provides risk of hepatic

decompensation over 5 years. The Amsterdam-Oxford model provide transplant free survival and included patients with small duct PSC and PSC-autoimmune hepatitis overlap, although there were very small numbers in each group.

MRI and VCTE are attractive as prognostic tools because they are frequently obtained during clinical care. The Anali score can be readily obtained from MRI of the abdomen with or without gadolinium because imaging is commonly obtained as part of clinical practice. Results from VCTE or MRE, including baseline measurements as well as annual changes can provide prognostic information, although data on VCTE and MRE are limited to those derived from retrospective studies.

A number of novel biomarkers involved in inflammation, fibrosis or the gut barrier have been studied that are not commercially available but may warrant further study, including third generation anti-neutrophil cytoplasmic antibodies to serine protease-3[40-44]. Future studies could combine results for the prognostic models that include clinical and laboratory data with scores from MRI and elastography (*e.g.* UK-PSC or PREsTo+Anali score+elastography score). As the test performance of these noninvasive prognostic models improve they may not only serve as surrogate endpoints in clinical trials, but they can also be used to inform our patients about their prognosis. Other cutting-edge techniques, including artificial intelligence may be employed to identify findings on imaging associated with disease progression, survival or patients at risk for cholangiocarcinoma[44].

CONCLUSION

In conclusion, a number of noninvasive prognostic models for PSC are available that can be used in clinical trials as surrogate endpoints or as tools to inform patients about their disease progression. The models can be tailored to a specific trial endpoint, such as PREsTo score for hepatic decompensation or UK-PSC score for transplant-free survival. In the future, combining these models with results from elastography may improve test performance. Other areas warranting further investigation include novel molecular diagnostics, composition of the gut microbiome and its association with clinical outcomes as well as exploring the role of artificial intelligence in identifying imaging findings associated with disease progression or cholangiocarcinoma.

FOOTNOTES

Author contributions: Russo MW collected and reviewed the articles and wrote the paper.

Conflict-of-interest statement: All the author has no conflicts of interest.

Country/Territory of origin: United States

ORCID number: Mark W Russo 0000-0001-8946-7296.

S-Editor: Liu JH
L-Editor: A
P-Editor: Yu HG

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World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2023 September 27; 15(9): 1021-1032

DOI: 10.4254/wjh.v15.i9.1021

ISSN 1948-5182 (online)

MINIREVIEWS

Toxicity of targeted anticancer treatments on the liver in myeloproliferative neoplasms

Shubhrat Purwar, Anam Fatima, Himashree Bhattacharyya, Lakshmi Venkata Simhachalam Kutikuppala, Matei-Alexandru Cozma, Bahadar Singh Srichawla, Leah Komer, Khulud Mahmood Nurani, Mihnea-Alexandru Găman

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: He YH, China; Sultana N, Bangladesh; Zhang X, United States

Received: May 28, 2023
Peer-review started: May 28, 2023
First decision: July 17, 2023
Revised: August 6, 2023
Accepted: August 18, 2023
Article in press: August 18, 2023
Published online: September 27, 2023

Shubhrat Purwar, Department of Internal Medicine, Grant Government Medical College, Mumbai 400008, Maharashtra, India

Anam Fatima, Department of Internal Medicine, Pandit Jawaharlal Nehru Memorial Medical College, Raipur 492001, Chhattisgarh, India

Himashree Bhattacharyya, Department of Community & Family Medicine, AIIMS Guwahati, Assam 781101, India

Lakshmi Venkata Simhachalam Kutikuppala, Department of General Surgery, Dr NTR University of Health Sciences, Vijayawada 521104, Andhra Pradesh, India

Matei-Alexandru Cozma, Mihnea-Alexandru Găman, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest 050474, Romania

Matei-Alexandru Cozma, Department of Gastroenterology, Colentina Clinical Hospital, Bucharest 020125, Romania

Bahadar Singh Srichawla, Department of Neurology, University of Massachusetts Chan Medical School, Worcester, MA 01655, United States

Leah Komer, Department of Psychiatry, University of Toronto, Toronto M5G 1V7, Ontario, Canada

Khulud Mahmood Nurani, Faculty of Health Sciences, University of Nairobi, Nairobi 30197-00100, Kenya

Mihnea-Alexandru Găman, Department of Hematology, Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest 022328, Romania

Corresponding author: Mihnea-Alexandru Găman, Doctor, MD, PhD, Doctor, Research Fellow, Researcher, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, 8 Eroii Sanitari Boulevard, Bucharest 050474, Romania. mihneagaman@yahoo.com

Abstract

The liver has a central role in metabolism, therefore, it is susceptible to harmful effects of ingested medications (drugs, herbs, and nutritional supplements). Drug-induced liver injury (DILI) comprises a range of unexpected reactions that occur

after exposure to various classes of medication. Even though most cases consist of mild, temporary elevations in liver enzyme markers, DILI can also manifest as acute liver failure in some patients and can be associated with mortality. Herein, we briefly review available data on DILI induced by targeted anticancer agents in managing classical myeloproliferative neoplasms: Chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, and myelofibrosis.

Key Words: Myeloproliferative neoplasms; Chronic myeloid leukemia; Myelofibrosis; Polycythemia vera; Essential thrombocythemia; Hepatotoxicity; Drug-induced liver injury

Core Tip: Drug-induced liver injury (DILI) comprises a range of unexpected reactions that occur after exposure to any type of medication. Patients diagnosed with classical myeloproliferative neoplasms (MPNs) (chronic myeloid leukemia, polycythemia vera, essential thrombocythemia or primary myelofibrosis) are often prescribed pharmacological agents that can lead to DILI. Herein, we examine the hepatotoxic potential of kinase inhibitors used in the treatment of classical MPNs with a focus on DILI diagnosis, management and prevention. In most cases, DILI can be successfully managed with dose interruptions or reductions and use of hepatoprotective agents, however, in some cases drug cessation may be warranted.

Citation: Purwar S, Fatima A, Bhattacharyya H, Simhachalam Kutikuppala LV, Cozma MA, Srichawla BS, Komer L, Nurani KM, Găman MA. Toxicity of targeted anticancer treatments on the liver in myeloproliferative neoplasms. *World J Hepatol* 2023; 15(9): 1021-1032
URL: https://www.wjgnet.com/1948-5182/full/v15/i9/1021.htm
DOI: https://dx.doi.org/10.4254/wjh.v15.i9.1021

INTRODUCTION

A brief overview of myeloproliferative neoplasms

Haematopoietic stem cells exhibit pluripotency and have the capacity to self-renew, resulting in myeloid or lymphoid cell lines which differentiate into mature blood cells. Overproduction of terminal myeloid cell lines in the bone marrow due to certain mutations in hematopoietic stem cells gives rise to a group of disorders known as myeloproliferative neoplasms (MPNs). MPNs are broadly classified into three categories: Philadelphia-positive MPNs, such as chronic myeloid leukemia (CML), classical Philadelphia-negative MPNs, such as polycythemia vera (PV), primary myelofibrosis (PMF) and essential thrombocythemia (ET), and non-classical Philadelphia-negative MPNs which include chronic neutrophilic leukemia, chronic eosinophilic leukemia-not otherwise specified and MPN-unclassifiable[1,2].

Epidemiology of MPNs

The incidence rate of CML has increased, whereas its age-standardized incidence rate decreased to 0.84 per 100000 individuals in 2019 from 0.96 in 1990. In addition, a slight increase in the incidence of CML cases has been observed in males *vs* females[3]. According to a systematic review of 20 studies from Europe, North America, Asia, and Australia which assessed the incidence rate of PV, the annual pooled incidence rate was 0.84 per 100000 individuals. There was no significant difference in the crude annual incidence between males and females[4]. Ten studies from Europe and North America reported the annual pooled incidence rate of 1.03 per 100000 inhabitants, with a higher pooled annual incidence in males compared to females[4]. PMF has the lowest incidence among classical Philadelphia-negative MPNs, with an annual pooled incidence of 0.47 per 100000 subjects and a higher incidence in males than females[4].

Pathophysiology of MPNs

CML is characterized by a reciprocal translocation between chromosomes 22 and 9, resulting in the fusion of the Abelson Murine Leukemia (ABL) 1 gene with the Breakpoint Cluster Region (BCR) gene. This generates a chimeric protein with constitutively active tyrosine kinase activity, which promotes cell growth and signaling through various downstream pathways[5]. The World Health Organization has divided the progression of CML into 2 phases primarily based on blast cell counts in the peripheral blood or bone marrow: Chronic phase and blast phase (≥ 20% myeloid blast cells in the bone marrow or peripheral blood or elevated numbers of lymphoid blast cells in the bone marrow or peripheral blood or evidence of extramedullary proliferation of blast cells), with the majority of patients presenting in the chronic phase[6]. There has been an increase in the life expectancy of CML patients, similar to that of the general population. This can be attributed to the fact that most newly diagnosed cases of CML occur in the chronic phase of the disease and due to the availability of new and effective therapies[7].

Classical Philadelphia-negative MPNs include PV, which primarily involves excess proliferation of red blood cells, ET, with thrombocytosis in the peripheral blood and overactive megakaryocytes in the bone marrow, and PMF, which involves fibrosis of the bone marrow and other diagnostic criteria. The pathogenesis of classical Philadelphia-negative

MPNs requires constitutive activation of the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway due to mutations in a variety of genes, out of which, JAK2V617F gain of function mutation is the most frequent, being present in > 95% of PV cases and > 50% of PMF and ET cases[8,9]. The remaining cases of PV are linked to JAK2 exon 12 mutations, while most of the remaining cases of PMF and ET have detectable MPL or CALR mutations[10]. Both ET and PV have a relatively favorable prognosis, with ET carrying the most favourable prognosis and PMF carrying the worst prognosis[11].

DRUG-INDUCED LIVER INJURY: BRIEF OVERVIEW

The liver is susceptible to the harmful effects of ingested medications (drugs, herbs, and nutritional supplements) because of its central role in metabolism[12,13]. Drug-induced liver injury (DILI) comprises a range of unexpected reactions occurring after exposure to various medications. Even though most cases consist of mild, temporary elevations in liver enzyme markers, DILI can result in acute liver failure (ALF). Thus, DILI may emerge as a significant cause of liver disease and sometimes lead to increased mortality rates[14-16].

The pathogenesis of DILI is complex and not fully understood. It can vary significantly between different individuals and based on the drugs that cause liver injury, which explains the wide range of phenotypic traits in clinical presentation and severity[17]. DILI results from a combination of genetic, non-hereditary, and environmental variables, and is often attributed to an allergic immune response[18].

The potential for multiple clinical presentations and the lack of specific biomarkers or biochemical tests often make the diagnosis difficult and delayed. Consequently, DILI must always be considered in patients who are prescribed medications and exhibit unexplained liver injury[17,19]. Moreover, DILI is the leading cause of drug withdrawal from the marketplace which can result in changes in drug costs and challenges in medication availability[20].

The pathophysiology of DILI is a complex, multistep process involving both direct injury and different inflammatory responses induced by either the drug itself, its metabolites, or the immune system. It denotes a combination of various host-related, environmental, and drug-related factors. If ALF does not occur, patients usually fully recover after an episode of DILI if the responsible medication is discontinued[12,18,21].

Among the main pathophysiological processes involved in the pathogenesis of DILI, one must highlight oxidative stress, interference with bile acids' transportation, alteration of mitochondrial biogenesis, and triggering of innate immune responses, necrosis, or even apoptosis[15,18].

Liver toxicity is further categorized as direct, indirect, or idiosyncratic based on the underlying mechanism of action of the chemical compound that leads to DILI. Direct hepatotoxicity is caused by agents which produce immediate and direct injury to the liver. This is a common, predictable, dose-dependent injury with a short latency period (1 to 5 d). It causes elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations, induces minimal or no symptoms, is associated with normal total bilirubin levels, and usually disappears once the drug is stopped or the dose is lowered[22,23].

Indirect hepatotoxicity is defined as "a condition caused by the medication's actions rather than from its inherent hepatotoxic effects or immunogenicity". This best translates to "what the drug does rather than what the drug is". This can either result in induction of a new liver condition or an exacerbation of a preexisting condition, *e.g.*, induction of immune-mediated hepatitis, reactivation of viral hepatitis or progression of fatty liver disease[12,22].

Idiosyncratic hepatotoxicity is caused by agents that have no direct hepatotoxic effect. It is an unpredictable condition, less common (< 1 of every 10000 exposed individuals), is not dose-related, has a longer latency period (up to several weeks), and a more variable clinical presentation[12,22,24].

A rapid diagnosis of DILI is crucial since one of the primary treatment interventions for hepatotoxicity is drug withdrawal. Moreover, establishing a DILI diagnosis can support the prevention of further adverse reactions through regulatory decisions such as prescription warnings or the removal of pharmaceuticals from the market[12,13,25].

In most cases, a diagnosis of DILI is one of exclusion since there is no specific test available for this entity. It is imperative to eliminate other causes of liver injury, *e.g.*, infectious hepatitis, acute alcoholic hepatitis, or ischaemic hepatitis. Suspicion of DILI arises from the discovery of alterations in standard liver function tests, *i.e.*, AST, ALT, total and direct bilirubin levels, serum albumin, alkaline phosphatase (ALP), or international normalized ratio[13].

Clinical manifestations, such as fatigue, nausea, malaise, right upper quadrant pain, pruritus, and jaundice, are non-specific and commonly encountered in various acute and chronic liver diseases. Liver imaging (abdominal ultrasonography, magnetic resonance cholangiography or computed tomography) is often used to exclude the presence of biliary obstruction and focal lesions. Liver biopsies are completed in less than half of suspected cases, and usually in instances where the evolution of the liver injury is not reversed after a suspected medication has been discontinued[22,26].

Currently, over 18 different histological aspects of DILI have been proposed, all of which are associated with varying degrees of inflammation, bile accumulation, ductopenia, steatohepatitis, macro- and micro-vesicular fatty depositions in the liver, pigment deposition, fibrosis or vascular congestion and obliteration[12,19].

DILI can also be classified by its biochemical pattern based on ALT and ALP levels. A pattern of hepatocellular damage is defined by an "elevation in ALT greater than 2 to 5 times the upper limit of normal (ULN) and/or by an ALT/ALP ratio also greater than 5". A pattern of cholestatic damage is defined by an "elevation in ALP greater than 3 times the ULN and/or an ALT/ALP ratio less than 2". A pattern of mixed hepatocellular/cholestatic damage is defined by "an increase in ALT greater than 2 to 5 times the ULN and an increase in ALP greater than 3 times the ULN and/or an ALT/ALP ratio between 2 and 5". These patterns have been proposed by the "American Association for the Study of Liver Diseases" and are summarized in Table 1[18,27,28].

Table 1 Biochemical classification of drug-induced liver injury

	Hepatocellular DILI	Mixed DILI	Cholestatic DILI
AASLD criteria for diagnosis of DILI	Elevation of ALT ≥ 3 times ULN and ALT/ALP ratio ≥ 5 times	ALT ≥ 3 times ULN, ALP ≥ 2 times ULN and ALT/ALP ratio < 5 but >2 times ULN	ALP ≥ 2 times ULN and ALT/ALP ratio of ≤ 2 times ULN
R value criteria for different patterns of DILI	R = (ALT/ULN)/(ALP/ULN) > 5	R = (ALT/ULN)/(ALP/ULN) < 5 and > 2	R = (ALT/ULN)/(ALP/ULN) < 2

ALP: Akaline phosphatase; ALT: Alanine Aminotransferase; DILI: Drug-induced liver injury; ULN: Upper limit of normal.

Management

While in some patients, DILI can spontaneously resolve without active treatment, in most cases, the hallmark of DILI treatment is the withdrawal of the offending drug. Clinical and biochemical alterations are expected to improve over several days or weeks. Since patients who develop jaundice are more likely to progress to ALF, these subjects usually require strict monitoring and hospitalization, particularly if DILI exhibits a hepatocellular phenotype. Treatment of DILI is usually supportive, with no other specific medications showing any significant benefit. However, there are many agents used for supportive purposes, *e.g.*, corticosteroids (empirically used by many clinicians), cholestyramine (administered to patients with acute liver injury caused by leflunomide), carnitine (an antidote for valproate-induced liver injury) or N-acetyl cysteine (NAC, a treatment for acetaminophen toxicity), silymarin, L-arginine, L-ornithine L-aspartate and/or vitamin E[13,29-32].

Prognosis

DILI typically resolves after discontinuing the offending drug and/or administering hepatoprotective agents. However, in rare cases, DILI may progress to ALF, with clinical features such as jaundice, ascites, encephalopathy, coagulopathy, and a mortality rate of 60% to 90% without liver transplantation[14,17].

Different scoring systems for predicting the prognosis of DILI have been proposed. The most validated and the one used by The Food and Drug Administration (FDA) during the drug development process to identify pharmacological agents that can potentially induce severe liver injury is "Hy's law". This was developed by Hyman Zimmerman in the 1960s, according to which 10% of the patients who develop jaundice will develop ALF. Other scores for predicting the severity of DILI are the Model for End-Stage Liver Disease score, King's college criteria score, and Acute Liver Failure Study Group index [12,13,19].

Older age, higher drug dosages, presence of liver disorders or cardiovascular comorbidities, African American ethnicity, and female sex have all been linked to an elevated risk of DILI and more severe forms. Still, there is little empiric data available to support that these variables are indeed risk factors for DILI or have an impact on its prognosis [33].

MAIN THERAPEUTIC AGENTS USED IN MPNS

The development of tyrosine kinase inhibitors (TKIs) following the discovery of the BCR-ABL chimeric gene has drastically improved the success rate of CML treatment. TKIs have improved the 10-year survival rate from 20% to 80%-90%[34]. Commonly used TKIs for the treatment of chronic phase CML involve first-generation TKIs (*e.g.*, imatinib), second-generation TKIs (*i.e.*, dasatinib, nilotinib, and bosutinib), and third-generation TKIs (*i.e.*, ponatinib). Imatinib was the first TKI to be approved by the FDA[35]. The IRIS trial first showed the high effectiveness of imatinib in increasing the survival rate of newly diagnosed CML patients compared to interferon-alpha plus cytarabine[34]. It is a fairly safe drug as long as patients are closely monitored. Second-generation TKIs exhibit rapid molecular responses and have been used in cases of resistance/intolerance to imatinib[36].

The discovery of the involvement of the JAK/STAT pathway in the pathogenesis of classical Philadelphia-negative MPNs paved the way for the TKIs to inhibit the JAK/STAT pathway. Ruxolitinib was the first targeted drug developed that inhibits both JAK1 and JAK2 and is approved for use in intermediate and high-risk myelofibrosis (MF) based on the COMFORT trials and in cases of PV resistant or intolerant to hydroxyurea based on the RESPONSE trial[37].

Fedratinib is another TKI inhibiting JAK2 and FMS-like tyrosine kinase 3 and is approved for treating intermediate or high-risk PMF or secondary MF. Diarrhea, nausea, and anemia are common side effects associated with this therapy. Renal function, liver enzymes, lipase, and amylase may require frequent monitoring during the treatment[38].

Momelotinib is a recently FDA-approved JAK1/JAK2 inhibitor that antagonizes the activin A receptor type 1. It is used to treat patients with MF with moderate/severe anemia[14]. It is similar to ruxolitinib but with the added advantage of improving anemia[12]. The most common side effects associated with it include diarrhea, peripheral neuropathy, dizziness, nausea, and thrombocytopenia[39].

In high-risk patients suffering from PV and ET, cytoreductive therapy with hydroxyurea and interferon alpha are first-line choices used to reduce the rate of thrombotic events. Hydroxyurea is a potent ribonucleotide reductase inhibitor causing inhibition of DNA synthesis and cell death[40].

Interferons, especially pegylated interferon α (peg-IFNα) and ropeg interferons, are increasingly employed as effective alternatives to cytoreduction with hydroxyurea in patients with ET and PV. Studies have reported a decrease in the JAK2V617F allele burden following the prescription of interferon-based therapy, which does not occur with hydroxyurea. Interferon is also used along with ruxolitinib in patients with low to intermediate-risk MF. Peg-IFNα and ropeg interferons are associated with a lower rate of adverse effects than standard interferons α used in the past[41].

EPIDEMIOLOGY OF DILI IN PATIENTS DIAGNOSED WITH MPNS

DILI is mainly characterized by increased liver enzyme concentrations due to damage induced to hepatocytes. Hepatotoxicity in CML subjects on TKI therapy presents as low-grade elevation of ALT and/or AST levels in about 25%-35% of cases, and high-grade elevation in about 2% of patients. The use of newer-generation TKIs (*e.g.* bosutinib, nilotinib, and ponatinib), has been associated with higher risks of liver toxicity[42].

DILI was a rare event in the 5-year follow-up of the phase 3 DASISION (Dasatinib Versus Imatinib Study in Treatment-Naïve CML Patients) trial, which compared the two aforementioned pharmacological agents. Therapy discontinuation was only required in the subgroup who received 400 mg of imatinib daily due to increases in ALT or AST concentrations (n = 1 each out of 258 individuals) and in one case of toxic hepatitis (n = 1). However, no subjects (n = 0 out of 258 individuals) discontinued treatment with 100 mg of daily dasatinib due to DILI[43].

In the ENESTnd trial, which compared the daily administration of 400 mg nilotinib (n = 277 patients) and 300 mg nilotinib (n = 279 patients) to each other, and to 400 mg imatinib (n = 280 patients) for the management of newly diagnosed CML, the investigators identified multiple cases of liver toxicity. Elevations in total bilirubin (n = 171, 62% *vs* n = 149, 53% *vs* n = 27, 10%), ALT (n = 203, 73% *vs* n = 186, 66% *vs* n = 57, 20%) and AST (n = 134, 48% *vs* n = 112, 40% *vs* n = 65, 23%) concentrations were more likely to occur in the 400 mg nilotinib and 300 mg nilotinib *vs* 400 imatinib group, respectively. In contrast, an increase in ALP (n = 76, 27% *vs* n = 59, 21% *vs* n = 92, 33%) value was more common in patients who received imatinib. However, grade 3/4 adverse events were rare and occurred predominantly in individuals who were prescribed nilotinib 400 mg or 300 mg *vs* imatinib 400 mg; all grades elevations occurred in total bilirubin (n = 21, 8% *vs* n = 10, 4% *vs* n = 1, < 1%), ALT (n = 25, 9% *vs* n = 11, 4% *vs* n = 7, < 2%) and AST (n = 8, 3% *vs* n = 4, 1% *vs* n = 3, 1%) values, respectively. Whereas a grade 3/4 increase in ALP only occurred in 1 case (< 1%) of imatinib-treated patients[44].

The NOVEL trial evaluated the safety and efficacy of nilotinib in 85 patients with imatinib intolerant/resistant CML. Their findings demonstrated that non-hematological adverse events occurring in correlation with the use of nilotinib manifested as elevations in ALT (n = 18, 21.2%), bilirubin (n = 12, 14.1%) and/or AST (n = 7, 8.2%) values. However, grade 3/4 elevations were rare and only 2 and 1 patients, respectively, experienced them in AST (2.4%) and/or ALT (1.2%) concentrations. In NOVEL, one patient with imatinib-induced liver toxicity required a switch of therapy to nilotinib, which resulted in DILI resolution. Serious DILI-related adverse events such as jaundice and chronic hepatitis have been reported[45].

The BYOND trial explored the benefits of 500 mg once daily of bosutinib for CML individuals (n = 163 subjects) who exhibited resistance and/or intolerance to other TKIs. DILI manifested only as elevations in AST (all grades n = 32, 19.6%) and/or ALT concentrations (all grades n = 42, 25.8%). However, grade 3/4 increases in ALT (n = 23, 14.1%) and/or AST (n = 7; 4.3%) were not common[46].

In the clinical trial which evaluated the benefits of bosutinib prescription in 119 CML subjects who failed to achieve satisfactory responses to imatinib and dasatinib and/or nilotinib, increases in AST/ALT values were noted in 16% of cases (13% classified as therapy-related), with only 6% of grade 3 adverse events and none severe/grade 4 side effects being noted. Elevations in these biochemical markers manifested early after drug initiation (approximately 81 d) and lasted approximately 29 d. DILI was successfully managed with dose interruptions, reductions, and/or use of hepatoprotective agents in 6, 5, and 1 CML case(s), respectively. Grade 3/4 DILI was more likely in CML individuals who received imatinib in the first six months following CML diagnosis and in subjects who exhibited elevated basophil counts[47].

Data from the CML registry in Belgium suggests that ponatinib-induced DILI cases are rare. Liver toxicity was uncommon in the 33 CML patients who received ponatinib and occurred in < 10% of treated individuals. Hepatocellular injury, hepatitis, and cholestasis were noted in 1 case each[48].

The PEARL study evaluated the safety and efficacy of ponatinib in CML subjects who experienced failure of 2 or more TKIs. Grade 1/2 non-hematological adverse events (including DILI) were highlighted in 19 (40%) of the 48 CML individuals enrolled. The investigators noticed no liver-related grade 3/4 adverse events[49].

Asciminib is a recently introduced TKI for managing CML, including T315I-mutated cases. This pharmacological agent inhibits the BCR-ABL1 protein in an allosteric manner, leading to an inactive conformation of its target. In a phase 1 trial of asciminib in heavily pretreated CML individuals, this novel medication led to elevation in ALT (n = 16, 10.7%; grade 3/4, n = 4, 2.7%), AST (n = 15, 10%; grade 3/4, n = 3, 2%) and gamma-glutamyltransferase (n = 12, 8%; grade 3/4, n = 3, 2%) concentrations, however, grade 3/4 liver-related adverse events occurred in < 3% of asciminib-treated subjects[50].

In the STAMP trial that investigated 40 mg of asciminib twice daily *vs* 500 mg of bosutinib once daily in individuals diagnosed with CML with ≥ 2 previous TKI therapies, DILI was more frequently noticed in the bosutinib group, *i.e.*, 27.6% (n = 21) and 21.1% (n = 16) of subjects experienced elevations in ALT and AST concentrations, respectively, *vs* 3.8% (n = 6) each in the asciminib group. Grade 3/4 adverse effects were more likely to present in bosutinib-prescribed subjects (14.5%, n = 11 for ALT; 6.6% n = 5 for AST) *vs* asciminib-treated subjects (3.8%, n = 6 for ALT and AST each). Significant elevations in ALT values necessitated treatment cessation in bosutinib-treated CML patients[51].

Ruxolitinib appears to be a safe option in terms of liver toxicity. Based on the findings of a double-blind, placebo-controlled trial assessing ruxolitinib in the management of MF classified as intermediate-2 or high-risk, DILI was not mentioned amongst the most common adverse side effects (experienced by at least 10% of the 155 enrolled subjects) caused by ruxolitinib[52].

Ruxolitinib was associated with an increase in ALT concentrations in around 6% of the MF patients and with high-grade elevations in only 1% of the individuals enrolled in the JUMP trial[53].

In the RuxoBeat trial, which investigated the benefits of ruxolitinib therapy in newly-diagnosed PV, 7 of 28 treated subjects (25%) experienced changes in biochemical markers, including DILI. However, only 3 cases of grade 3 adverse events were reported, out of which 2 consisted of elevations in AST/ALT concentrations and required reduction of the prescribed dose. However, no patient necessitated interruption of ruxolitinib[54].

Similarly, the assessment results conducted by Vannucchi *et al*[55] only indicate minor changes in ALT/AST values following ruxolitinib administration in individuals diagnosed with PV.

The EXPAND trial assessed the safety and efficacy of ruxolitinib in individuals with MF and thrombocyte counts between 50000/mmc and 100000/mmc. In this investigation, a total of 5 cases of elevations in bilirubin values were noticed: 1 of the 18 patients who had platelets < 75000/mmc but > 50000/mmc and 4 of the 20 patients who had platelets < 100000/mmc but > 75000/mmc. However, of these, only two grade 3 or more increases in bilirubin levels were highlighted, all were reported in patients with thrombocyte counts < 100000/mmc but > 75000/mmc[56].

In a clinical trial that explored the co-administration of ruxolitinib and interferon alpha-2 for the management of PV and MF, grade 1/2 liver-related adverse events, *i.e.*, an increase in AST and lactate dehydrogenase values, were noted in 7 (14%) and 17 (34%) of the 50 patients receiving therapy, with no cases of grade 3-4 side effects occurring in neither subjects with PV nor MF[57].

The JAKARTA trial compared fedratinib *vs* placebo elevations of liver enzymes were detected in 40%-60% of the subjects; however, ≥ 3 grade elevations in these serum markers were not common. In JAKARTA, 96 subjects were assigned to receive 400 mg of fedratinib daily, 97 to receive 500 mg/day of the same drug, and 95 individuals received placebo pills. All grade elevations in ALT (fedratinib 400 mg: 53%; fedratinib 500 mg: 46%; placebo: 17%) and AST (fedratinib 400 mg: 60%; fedratinib 500 mg: 48%; placebo: 29%) concentrations were frequently detected in the fedratinib subgroups *vs* placebo, whereas bilirubin levels were more likely to increase in the placebo group (fedratinib 400 mg: 31%; fedratinib 500 mg: 28%; placebo: 40%)[58]. However, grade 3-4 increases in ALT values were only noted in 3% of the fedratinib 400 mg and 500 mg subgroups each *vs* 0% in the placebo group. Grade 3-4 increases in AST values were only noted in 2% of the fedratinib 400 mg and 500 mg subgroups each *vs* 1% in the placebo group, whereas grade 3-4 elevations in bilirubin concentrations occurred in 2% of the placebo group and fedratinib 400 mg subgroups and in 1% of the fedratinib 500 mg subgroup, respectively[58].

Momelotinib therapy in MF was also associated with cases of liver toxicity, *i.e.*, grade 3-4 increases in ALT concentrations in 4% of patients and in AST and ALP concentrations in 2% of patients each[59]. Grade 1-2 increases in AST (21%), ALT (19%), and bilirubin (13%) concentrations were also detected[59]. In an integrated assessment of momelotinib based on data derived from phase 3 randomized clinical trials, Verstovsek *et al*[60] also highlighted that of the 725 individuals with MF who received the drug, nine subjects (1.2%) experienced notable elevations in ALT values requiring dose interruption/reduction or momelotinib discontinuation. When momelotinib was studied for PV and/or ET, no occurrences of liver damage were reported in either cohort[61].

Ropeg interferons are relatively safer drugs than previously used interferons with respect to liver toxicity. When peg-IFNα-2a was tested in the management of PV (n = 40) and ET (n = 39), grade 3 increases in liver function tests were reported in 5% (n = 2) and 8% (n = 3) of the PV and ET subgroups, respectively. No grade 4 side effects were reported [62]. In a trial exploring the safety and benefits of peg-IFNα-2b in PV and ET, elevations in liver enzymes were among the most frequent non-hematological side effects. In total, 2 subjects required peg-IFNα-2b discontinuation due to elevations in AST and ALT values[63].

DILI IN MPNS

Data on risk factors for DILI in patients living with MPNs are scarce. However, several studies have identified potential risk factors associated with an increased risk of imatinib/TKI-induced hepatotoxicity, namely[64-66]: (1) Use of proton pump inhibitors (3.8- fold increased risk): Imatinib is both a substrate and an inhibitor of the ABCG2 which is a drug efflux pump expressed on various body tissues, including the liver. Thus, the inhibition of this pump leads to increased drug concentrations in liver cells, thus increasing the risk of hepatotoxicity. Moreover, proton pump inhibitors are hepatotoxic on their own; (2) Presence of liver disease or HBV carrier state (8-fold elevated risk): Imatinib is metabolized by the liver; therefore, liver impairment or HBV carrier state may increase its plasma levels due to ineffective drug metabolism; (3) Drug dose > 400 mg (2.3-fold increased risk): Higher plasma levels of imatinib can enhance the risk of liver toxicity; (4) Body weight of < 55 kg (2.2-fold increased risk): The dose of imatinib is chosen based on the phase of the disease and not based on body surface area; (5) Concomitant use of acetaminophen: Acetaminophen itself is hepatotoxic; (6) Use of alcohol: Alcohol acts as a cytochrome oxidase enzyme inducer, thereby increasing the levels of toxic metabolites; and (7) Use of hepatotoxic drugs.

The relative risk of DILI seems higher with the prescription of 2nd & 3rd generation TKIs compared to 1st generation pharmacological agents (imatinib)[67]. The average duration from drug initiation to DILI development with TKIs was 2-6 mo, whereas with the use of ruxolitinib, it was 1-6 mo[68,69]. In most cases, the diagnosis of DILI was established after the virology panel results for hepatitis B, human immunodeficiency virus, cytomegalovirus and Epstein-Barr virus

infections came in negative. Autoimmune antibody testing, abdominal ultrasound, liver biopsy, and toxicology screening (alcohol, illicit drugs, acetaminophen) were also performed in conjunction with liver function tests to exclude other causes of liver injury[70,71]. Liver biopsy is usually not preferred to provide diagnostic information regarding liver injury but is considered for the staging of fibrosis[72]. In some instances, genetic testing for hereditary conditions, such as hemochromatosis or Wilson's disease, maybe required[73]. Pharmacogenomics assessments for mutations/polymorphisms in human leukocyte antigen genes, drug-metabolizing enzymes, ATP-binding cassette and/or solute carrier transporters, may also be required to understand why certain individuals develop DILI[74].

However, investigations on DILI in subjects with MPNs remain scarce and the pathogenesis of DILI induced by targeted anticancer agents warrants further consideration in future studies. For example, researchers could investigate the impact of oxidative stress, immunity, and bile acid metabolism on the emergence of DILI in individuals with MPNs. As such, DILI still remains a diagnosis of exclusion, with the recommended biochemical criteria being as follows[72,73]: (1) ALT values ≥ 5 ULN; (2) AST values ≥ 3 ULN; (3) ALP values ≥ 2 ULN; and (4) total bilirubin ≥ 2 ULN.

A common tool used for the diagnosis of DILI is the Roussel Uclaf Causality Assessment Method. It is based on 7 factors, including the onset of reaction, clinical response after withdrawal or continuation of the drug, response to re-administration of the drug, temporal relationship, risk factors, concomitant drug use, and absence of any non-drug etiologies[75].

Management of DILI in MPNs

In most cases, discontinuation of the offending drug in individuals with clinically established hepatotoxicity and/or administration of hepatoprotective agents has been found to normalize liver enzymes within a few weeks. In cases of severe liver injury, resolution has been achieved by treatment with high-dose steroids for a few weeks. For example, imatinib therapy can be resumed with dose reductions or with co-administration of low doses of steroids if hepatotoxicity occurs[76]. The European LeukemiaNet has established guidelines for the management of TKI-induced liver injury[77] (Figure 1).

Since CML patients often require lifelong treatment, Lopina *et al*[78] have suggested a novel score-based decision algorithm (Table 2) for restarting TKIs after acute imatinib-induced liver injury and for the choice of 2nd generation TKIs. The score takes into account: (1) The grade of hepatotoxic reaction; (2) the grade of response to the use of imatinib, *i.e.*, the presence of early molecular response (EMR) to imatinib therapy at 3 mo (3-month BCR-ABL1 ≤ 10% according to the international scale). This is not applicable if imatinib treatment was prescribed for < 3 mo; (3) the grade of response to the use of imatinib, *i.e.*, the presence of EMR to imatinib therapy at 6 mo (6-month BCR-ABL1 < 1% according to the international scale). This is not applicable if hepatotoxicity developed in <6 mo of imatinib therapy; (4) the presence of a liver offender (concomitant use of another drug that probably caused drug interactions); and (5) the presence of viral hepatitis reactivation identified by polymerase chain reaction.

The approach to restart imatinib can be based on the score listed above[78] as follows: (1) Score = 0 points: Withdraw the drug and switch to 2nd generation TKIs; (2) Score = 1 point: It is preferred to withdraw imatinib if the patient requires treatment for > 6 mo; and (3) Score ≥ 2 points: Restart imatinib after resolution of DILI.

The choice of a 2nd generation TKI is based on the presence of comorbidities and/or BCR-ABL1 kinase domain mutations[78].

Other cases of DILI in CML patients require special consideration. For example, reactivation of hepatitis B infection often undergoes spontaneous resolution but treatment with antiviral agents (tenofovir and entecavir) is sometimes needed. Moreover, liver transplantation can be successful in imatinib-induced fulminant liver failure[70].

In patients who develop hepatotoxicity while on ruxolitinib, abrupt drug discontinuation should be avoided as it can lead to potentially fatal withdrawal symptoms. Therefore, dose reduction should be completed gradually. Tremblay *et al* [79] recommends liver biopsy for adaptive management in patients with evidence of hepatocellular damage potentially caused by the use of ruxolitinib.

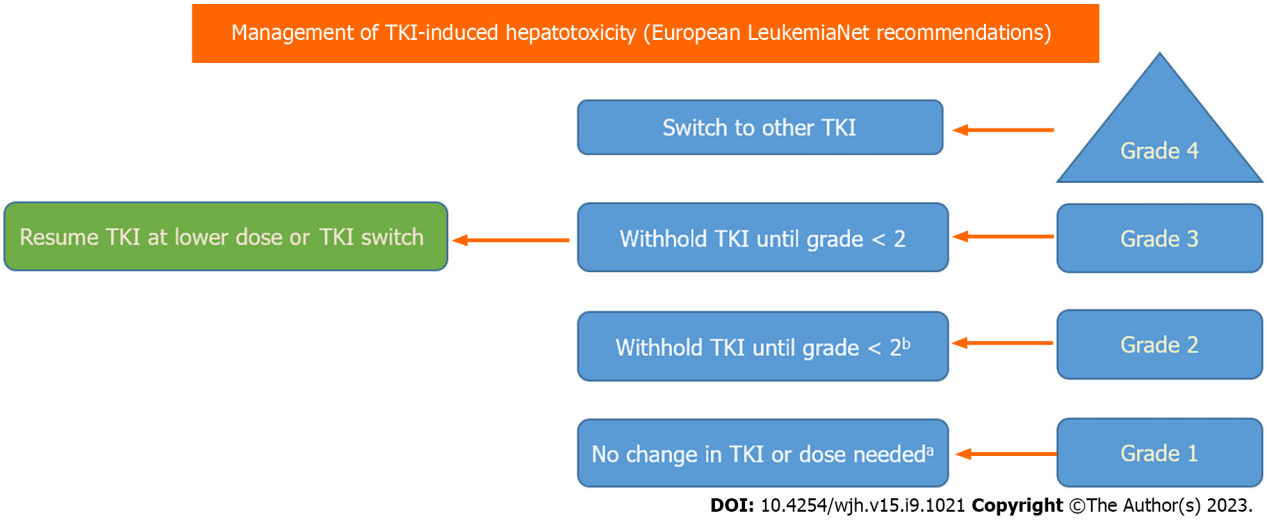
Prevention of DILI in MPNs

The relatively limited number of particular treatments and antidotes that are currently available restricts the medical therapy of acute DILI. The primary therapeutic strategy for DILI remains discontinuing the alleged harmful substance [80]. When NAC is administered within 4 to 16 h after an acute acetaminophen overdose, hepatotoxicity is effectively avoided. NAC is less helpful for ALF caused by non-acetaminophen drugs[81]. First-line prevention measures include avoiding the use of potentially hepatotoxic medications in patients with an underlying chronic liver disease or who have been identified as having a genetic, or other risk factors for developing DILI. Other measures include monitoring ALT, AST, and other liver-associated enzymes (ALP, bilirubin, *etc.*) to detect hepatotoxicity for particular medications early on. In some developed countries, regulating the availability of potentially dangerous amounts of acetaminophen has proven effective in reducing overdoses[82]. To prevent purposeful and inadvertent overdoses, improvements in abeling and patient education are still required in countries with unlimited access to acetaminophen. The significance of the gut microbiota in preventing DILI will likely continue to be understood, allowing for the development of new therapeutic strategies. Its ability to guard against acetaminophen-induced and other types of acute DILI is currently being investigated[83]. Thus, in patients diagnosed with MPNs who are started on potentially hepatotoxic agents, we recommend checking liver function tests before therapy initiation and regularly during treatment. Moreover, the management of each case should be tailored to the comorbidities and concurrent medications of the patient, especially in subjects who suffer from MPNs and exhibit a high burden of cardiometabolic disorders[84]. Thus, DILI can be avoided in some instances. Further research should focus on identifying new hepatoprotective agents that could enable clinicians to overcome DILI and avoid drug cessation or dose reductions/interruptions which aid in the resolution of liver toxicity but might impact the treatment of the hematological malignancy.

Table 2 Novel score for the decision of restarting or withdrawing imatinib in chronic myeloid leukemia[78]

Factors	Imatinib restart[1]	Imatinib withdrawal
Grade of hepatotoxic reaction		
Grade 1	+	-
Grade 2	+[2]	-
Grade 3	+/-[3]	+/-
Grade 4 or presence liver transplantation or imatinib-induced liver cirrhosis or viral hepatitis reactivation	-	+
Presence of EMR to imatinib at 3 mo = BCR-ABL1^{IS} ≤ 10%		
Yes	+	-
No	-	+
Presence of EMR to imatinib at 6 mo = BCR-ABL1^{IS} < 1% (if applicable[4])		
Yes	+	-
No	-	+
Use of another drug that might cause liver toxicity		
Yes	+	-
No	-	+
Diagnosis of viral hepatitis established by PCR		
Yes	+	-
No	-	+

[1]Decide whether to restart imatinib only after resolution of acute hepatitis and normalization of liver function tests.
[2]Restart imatinib at a reduced or at the same dose.
[3]Restart imatinib if liver toxicity resolves in ≤ 1 month and there is no sign of recurrence.
[4]Do not take into consideration this factor if liver toxicity develops ≤ 6 months after imatinib initiation.
+: 1 point/yes; -: 0 points/no; ABL: Abelson Murine Leukemia; BCR: Breakpoint Cluster Region; EMR: Early molecular response; PCR: Polymerase chain reaction.



DOI: 10.4254/wjh.v15.i9.1021

Figure 1 Management of tyrosine kinase inhibitor-induced hepatotoxicity according to European LeukemiaNet recommendations. [a]Adverse events may require specific treatment; [b]Alternatively, continue TKI for 1 wk with appropriate management of adverse event. If no resolution is achieved, withhold TKI until liver toxicity is grade < 2 and monitor weekly. TKI: Tyrosine kinase inhibitor.

CONCLUSION

Data on liver toxicity induced by targeted anticancer therapy in MPNs is scarce; however, the use of TKIs has been linked to hepatotoxicity and/or DILI in CML, PV, ET, and MF in clinical trials and real-world data. Minor liver injury can be managed with drug discontinuation and/or dose reductions/interruptions and the administration of hepatoprotective agents. Careful consideration must be given in cases of severe hepatotoxicity.

FOOTNOTES

Author contributions: Purwar S, Fatima A, Bhattacharyya H, Simhachalam Kutikuppala LV, Cozma MA and Gaman MA reviewed the literature and drafted the manuscript; Srichawla BS, Nurani KM and Komer L edited the manuscript; Cozma MA and Gaman MA provided overall intellectual input, reviewed the literature, and edited the final version of the manuscript; all authors approved the final version to be published.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country/Territory of origin: Romania

ORCID number: Lakshmi Venkata Simhachalam Kutikuppala 0000-0002-5685-6049; Matei-Alexandru Cozma 0000-0002-4998-0105; Mihnea-Alexandru Găman 0000-0001-7133-8875.

S-Editor: Lin C
L-Editor: A
P-Editor: Yu HG

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World Journal of Hepatology

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World J Hepatol 2023 September 27; 15(9): 1033-1042

DOI: 10.4254/wjh.v15.i9.1033

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Liver transplant in patients with primary sclerosing cholangitis: A retrospective cohort from Northeastern Brazil

Louyse Teixeira de Souza Freitas, Elodie Bomfim Hyppolito, Victor Leonardo Barreto, Luiz Humberto Jataí Castelo Júnior, Bianca Carneiro de Melo Jorge, Frederico César Tahim de Sousa Brasil Háteras, Malthus Barbosa Marzola, Clébia Azevedo Lima, Raquel Mendes Celedonio, Gustavo Rêgo Coelho, Jose Huygens Parente Garcia

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Filipec Kanizaj T, Croatia; Janczewska E, Poland

Received: May 7, 2023
Peer-review started: May 7, 2023
First decision: June 7, 2023
Revised: July 7, 2023
Accepted: August 25, 2023
Article in press: August 25, 2023
Published online: September 27, 2023

Louyse Teixeira de Souza Freitas, Elodie Bomfim Hyppolito, Clébia Azevedo Lima, Raquel Mendes Celedonio, Gustavo Rêgo Coelho, Jose Huygens Parente Garcia, Liver Transplant Department, Walter Cantídio Teaching Hospital, Fortaleza 60430270, Ceará, Brazil

Elodie Bomfim Hyppolito, Victor Leonardo Barreto, Luiz Humberto Jataí Castelo Júnior, Bianca Carneiro de Melo Jorge, Frederico César Tahim de Sousa Brasil Háteras, Malthus Barbosa Marzola, School of Medicine, University of Fortaleza, Fortaleza 60811905, Ceará, Brazil

Elodie Bomfim Hyppolito, Hospital São José, Ceará State Health Department, Fortaleza 60455610, Ceará, Brazil

Gustavo Rêgo Coelho, Jose Huygens Parente Garcia, Department of Surgery, Federal University of Ceará, Fortaleza 60430140, Ceará, Brazil

Gustavo Rêgo Coelho, Jose Huygens Parente Garcia, Surgery Department, São Carlos Hospital, Fortaleza 60130241, Ceará, Brazil

Corresponding author: Louyse Teixeira de Souza Freitas, BSc, Nurse, Liver Transplant Department, Walter Cantídio Teaching Hospital, 1142 Coronel Nunes de Melo Street, Fortaleza 60430270, Ceará, Brazil. louyseteixeira.s@gmail.com

Abstract

BACKGROUND

Primary sclerosing cholangitis (PSC) manifests within a broad ethnic and racial spectrum, reflecting different levels of access to health care.

AIM

To evaluate the clinical profile, complications and survival rates of patients with PSC undergoing liver transplantation (LTx) at a Brazilian reference center.

METHODS

All patients diagnosed with PSC before or after LTx were included. The medical records were reviewed for demographic and clinical variables, including outcomes and survival. The level of statistical significance was set at $P < 0.05$.

RESULTS

Our cohort represented 1.6% (n = 34) of the 2113 patients receiving liver grafts at our service over the past two decades. Most were male (n = 19; 56%). The average age (40 ± 14 years) was similar for men and women (P = 0.347). The mean follow-up time from diagnosis to LTx was 68 mo. Most patients had the classic form of PSC. Three women had PSC/autoimmune hepatitis overlap syndrome, and one patient had small-duct PSC. Alkaline phosphatase levels at diagnosis and pre-LTx model for end-stage liver disease. scores were significantly higher in males. Inflammatory bowel research (IBD) was investigated by colonoscopy in 26/34 (76%) and was present in most cases (18/26; 69%). IBD was less common in women than in men (44.4% *vs*. 55.6%) (P = 0.692). Cholangiocarcinoma (CCA) was diagnosed in 2/34 (5.9%) patients by histopathology of the explant (survival: 3 years 6 mo, and 4 years 11 mo). Two patients had complications requiring a second LTx (one after 7 d due to hepatic artery thrombosis and one after 17 d due to primary graft dysfunction). Five patients (14.7%) developed biliary stricture. The overall median post-LTx survival was 66 mo. Most deaths occurred in the first year (infection n = 2, primary liver graft dysfunction n = 3, unknown cause n = 1). The 1-year and 5-year survival rates of this cohort were 82.3% and 70.6%, respectively, matching the mean overall survival rates of LTx patients at our center (87.1% and 69.43%, respectively) (P = 0.83).

CONCLUSION

Survival after 1 and 5 years was similar to that of other LTx indications. The observed CCA survival rate suggests CCA may be an indication for LTx in selected cases.

Key Words: Primary sclerosing cholangitis; Epidemiology; Liver transplantation; Survivor; Clinical associations; Pathological features

Core Tip: We present a case series of liver transplantation (LTx) patients from the largest center in Northeastern Brazil, with epidemiological features different from what is expected for primary sclerosing cholangitis (PSC) (*e.g.*, early manifestation and proportion of female patients). The finding of two cases of cholangiocarcinoma (CCA) with good survival is relevant to the discussion on the eligibility of selected cases of CCA for LTx. The survival of PSC patients was similar to that of LTx patients with other etiologies.

Citation: Freitas LTS, Hyppolito EB, Barreto VL, Júnior LHJC, Jorge BCM, Háteras FCTSB, Marzola MB, Lima CA, Celedonio RM, Coelho GR, Garcia JHP. Liver transplant in patients with primary sclerosing cholangitis: A retrospective cohort from Northeastern Brazil. *World J Hepatol* 2023; 15(9): 1033-1042

URL: https://www.wjgnet.com/1948-5182/full/v15/i9/1033.htm

DOI: https://dx.doi.org/10.4254/wjh.v15.i9.1033

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic, progressive autoimmune disease causing inflation, stenosis and dilation of the intra- and extrahepatic bile ducts[1]. Clinically characterized mainly by fatigue and pruritus[2], PSC may lead to cholangiocarcinoma (CCA) and cirrhosis. Around 70% of PSC patients have inflammatory bowel disease (IBD), especially ulcerative colitis, with elevated risk of colorectal cancer[3]. Currently available clinical treatments do not alter the natural history of PSC, and liver transplantation (LTx) is the only curative treatment available[4], although some studies have reported a post-LTx relapse rate of as much as 25%[5]. Intractable pruritus, recurrent cholangitis, hepatocarcinoma and decompensated cirrhosis are some of the classic indications for LTx[1], but the ideal moment for transplantation can be difficult to determine. The purpose of this study was to evaluate the clinical profile, complications and survival rates of PSC patients submitted to LTx at a Brazilian referral center.

MATERIALS AND METHODS

In this retrospective observational cohort study, we included all LTx patients diagnosed with PSC before or after transplantation. The diagnosis was based on clinical and laboratory findings confirmed by magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). Between May 2012 and May 2022, the LTx team at our service (Hospital Universitário Walter Cantídio, Federal University of Ceará, partnered with Hospital São Carlos) performed 2113 procedures; 34 of which (1.6%) were due to PSC. The study variables were age, sex, clinical manifestations, association with IBD and other comorbidities, time between diagnosis of PSC and LTx, cause of

LTx, PSC classification, laboratory findings, treatments and complications prior to LTx, time of ischemia, Child–Pugh and model for end-stage liver disease (MELD) scores, immunosuppression, PSC relapse following LTx, rejection, and death.

Histopathological diagnosis of small-duct PSC was considered when liver biopsy was performed prior to LTx or in the explant biopsy. Small-duct PSC was defined as cholestasis associated with a compatible liver biopsy, in the absence of biliary stricture on ERCP or MRCP. Autoimmune hepatitis (AIH) was diagnosed using the International AIH Group Score[6].

PSC relapse was defined as the presence on ERCP or MRCP of biliary stricture post-LTx at a site other than the anastomosis. The follow-up time was defined as the time of outpatient follow-up until the moment of inclusion in the study, or death.

The study protocol was approved by the Research Ethics Committee of the Federal University of Ceará and filed under #CAAE 98627218.6.2018.5045.

The level of statistical significance was set at 5% ($P < 0.05$). Non-normally distributed data were analyzed with the Mann–Whitney U test, while the χ^2 test and Fisher's exact test were used for categorical variables. Cumulative survival rates at the 95% confidence interval were estimated with Kaplan–Meier survival analysis.

RESULTS

Male sex was slightly predominant (n = 19; 56%). The average age was 40 ± 14 years, with no significant difference between men (38 ± 14 years) and women (43 ± 13 years) (P = 0.347). The mean MELD score was 24.1 ± 4.7 for men and 19.9 ± 8.1 for women (P = 0.011). The average time from onset of symptoms to diagnosis was 23 mo (range: 0–128 mo). The mean follow-up time from diagnosis to LTx was 68 mo (range: 0–196 mo). Classic PSC was the most frequently observed clinical form. Three women had AIH–PSC overlap syndrome, and one patient had small-duct PSC. All patients were symptomatic at diagnosis (Table 1).

Nearly all patients (n = 27; 93%) were treated with ursodeoxycholic acid (UDCA) and half (n = 14; 52%) used prednisone. All users of prednisone had overlap with AIH, with a predominance of the female sex (75%; P = 0.031). Endoscopic treatment was administered significantly more often to men (88%) than to women (12%) (P = 0.010). Alkaline phosphatase levels at diagnosis and pre-LTx MELD scores were significantly higher in males. The baseline and pre-LTx laboratory findings are shown in Table 2.

IBD was investigated by colonoscopy in 26 (76%) of 34 patients, and was present in most cases (18/26; 69%). The development of IBD was less common in women (44.4%) than in men (55.6%) (P = 0.692).

The mean age of PSC patients at the time of IBD diagnosis was 35 ± 14 years (median: 32 years). PSC and IBD were diagnosed simultaneously in two (11%) patients. PSC was diagnosed before IBD (range: 1–6.8 years; median: 3 years) in 6/18 (33%), and after IBD (range: 0.5–32 years; median 9.8 years) in 10/18 (56%). Patients without IBD (MELD: 24.6 ± 5.3) were significantly more severe at the time of LTx than patients with some form of IBD (19.3 ± 4.7) (P = 0.033). Table 3 shows the patients' clinical variables according to the presence/absence of IBD.

Diabetes mellitus (DM) was the most frequent comorbidity (n = 7; 22%), followed by systemic arterial hypertension and alcoholism (n = 6; 19%), dyslipidemia and smoking (n = 4; 12%), obesity (n = 1; 3.1%) and others (n = 3; 9%). DM was more frequent in patients without IBD (n = 4; 80%) than in patients with IBD (n = 1; 20%) (P = 0.030). Although frequently associated with PSC, ankylosing spondylitis and seronegative arthritis were not observed in this series. Information on densitometry was available for only four (12.5%) patients, although seven (21%) patients were undergoing treatment for osteoporosis.

Two techniques were used for bile duct reconstruction: end-to-end anastomosis (65%) and Roux-en-Y hepaticojejunostomy (35%). The former was preferred in patients with macroscopically normal common bile ducts.

CCA was diagnosed in two (5.9%) of 34 patients upon the histopathological examination of the explant, with the following characteristics.

Case 1: 47-year old man. Explant with nodule measuring 3.0 cm 2.5 cm 2.5 cm, with periductal and neural involvement, involvement of the liver hilum and intrahepatic bile ducts, vascular invasion and compromised margins (pT2bN2). The patient was peremptorily treated with capecitabine for 6 mo after LTx, but after 2 years and 4 mo experienced a recurrence of the neoplasm in the inferior vena cava, pancreas and lung. At this point, immunosuppression was reduced and 10 sessions of systemic chemotherapy with gemcitabine/cisplatin were administered but without response. Following that, the liver hilum and chest were submitted to radiotherapy. After 3 years and 6 mo, the patient presented neoplastic obstruction of the biliary tract for which a metallic prosthesis was inserted. The patient continues to use oral capecitabine and presents an excellent overall condition and quality of life, despite the relapse, with a survival of 4 years and 11 mo.

Case 2: 40-year old man. Intraoperative diagnosis of nodule, later confirmed in the explant to be an adenocarcinoma with biliary pattern measuring 2.8 cm 2.5 cm, with infiltration of the liver parenchyma, lymphovascular and perineural invasion, and compromised margins (pT2bN2). After 1 year, the patient experienced a recurrence of the neoplasm in the hepatic artery and lung. Chemotherapy with capecitabine for 6 mo and local radiotherapy were administered. The patient developed biliary obstruction for which a metallic prosthesis was inserted. Currently, the patient is clinically well, with a survival of 3 years and 10 mo.

As for complications of LTx, two patients required a second transplant, one after 7 d due to hepatic artery thrombosis and one after 17 d due to primary graft dysfunction. Five (14.7%) patients developed biliary stricture (end-to-end, n = 3; Roux-en-Y, n = 2), treated with ERCP and percutaneous drainage, respectively. Two patients had post-LTx relapse of PSC, with the appearance of intrahepatic biliary stricture confirmed on MRCP at 11 years and 7 mo (survival: 14 years

Table 1 Clinical and socioepidemiological variables of patients with primary sclerosing cholangitis submitted to liver transplantation between 2012 and 2022

Variables	*n*	Total[1]	Females (*n* = 14[1])	Males (*n* = 19[1])	*P* value[2]
Age at LTx, yr	32	40 ± 14 (36)	43 ± 13 (39)	38 ± 14 (35)	0.347
Age at first symptom, yr	30	32 ± 14 (30)	35 ± 13 (36)	30 ± 14 (29)	0.498
Age at IBD diagnosis, yr	17	35 ± 14 (32)	37 ± 18 (42)	33 ± 12 (30)	0.370
Months between 1st symptom and 1st consultation	26	18 ± 37 (2)	16 ± 33 (3)	19 ± 39 (2)	0.616
Months between onset of symptoms and diagnosis	31	80 ± 235 (23)	148 ± 357 (56)	31 ± 41 (13)	0.155
Baseline clinical symptoms					
Jaundice	32	29 (91%)	11 (85%)	18 (95%)	0.552
Pruritus	32	25 (74%)	6 (24%)	19 (76%)	
Fever + shivering	32	14 (44%)	5 (38%)	9 (47%)	0.618
Weight loss	32	18 (56%)	9 (69%)	9 (47%)	0.221
Fatigue	32	13 (41%)	6 (46%)	7 (37%)	0.598
PSC classification					
Classic PSC	31	30 (97%)	12 (92%)	18 (100%)	0.419
PSC + AIH	31	3 (9.7%)	3 (23%)	0 (0%)	0.064
Small-duct PSC	31	1 (3.2%)	0 (0%)	1 (5.6%)	> 0.999
Diagnostic testing					
MRCP realized	32	23 (72%)	10 (77%)	13 (68%)	0.704
MRCP	32	20 (62%)	10 (77%)	10 (53%)	0.163
ERPC	32	12 (38%)	3 (23%)	9 (47%)	0.163
Biopsy	31	20 (65%)	7 (54%)	13 (72%)	0.449
Comorbidities					
Diabetes	32	7 (22%)	2 (15%)	5 (26%)	0.671
Hypertension	32	6 (19%)	4 (31%)	2 (11%)	0.194
Dyslipidemia	32	4 (12%)	2 (15%)	2 (11%)	> 0.999
Obesity	32	1 (3.1%)	0 (0%)	1 (5.3%)	> 0.999
Smoking	32	4 (12%)	2 (15%)	2 (11%)	> 0.999
Drinking	32	6 (19%)	2 (15%)	4 (21%)	> 0.999
Others	31	8 (26%)	2 (17%)	6 (32%)	0.433
IBD	18				> 0.999
Ulcerative rectocolitis		15 (83%)	7 (88%)	8 (80%)	
Crohn's disease		3 (17%)	1 (12%)	2 (20%)	
Ankylosing spondylitis	32	0 (0%)	0 (0%)	0 (0%)	
Seronegative arthritis	32	0 (0%)	0 (0%)	0 (0%)	
Gallbladder calculus	32	7 (22%)	3 (23%)	4 (21%)	> 0.999
Gallbladder polyps	31	0 (0%)	0 (0%)	0 (0%)	
Neoplasia	31	4 (13%)	2 (15%)	2 (11%)	> 0.999
Dyslipidemia	32	4 (12%)	2 (15%)	2 (11%)	> 0.999
Obesity	32	1 (3.1%)	0 (0%)	1 (5.3%)	> 0.999
Smoking	32	4 (12%)	2 (15%)	2 (11%)	> 0.999

Drinking	32	6 (19%)	2 (15%)	4 (21%)	> 0.999
Other	31	8 (26%)	2 (17%)	6 (32%)	0.433
Treatment					
Ursodeoxycholic acid	29	27 (93%)	11 (92%)	16 (94%)	0.665
Prednisone	27	14 (52%)	9 (75%)	5 (33%)	0.031
Endoscopic treatment	16	8 (50%)	1 (12%)	7 (88%)	0.010
Indication for LTx					> 0.999
Untreatable pruritus		4 (12%)	2 (15%)	2 (11%)	
Decompensated cirrhosis		27 (84%)	11 (85%)	16 (84%)	
Hepatocellular carcinoma		1 (3.1%)	0 (0%)	1 (5.3%)	
Dominant stenosis	26	4 (15%)	1 (9.1%)	3 (20%)	0.614

[1]Range; mean ± SD (median); *n* (%).
[2]Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test; Pearson's χ^2 test.
AIH: Autoimmune hepatitis; ERCP: Endoscopic retrograde cholangiopancreatography; IBD: Inflammatory bowel disease; LTx: Liver transplantation; PSC: Primary sclerosing cholangitis; MRCP: Magnetic resonance cholangiopancreatography.

Table 2 Baseline and pretransplantation laboratory findings of patients with primary sclerosing cholangitis

Variables	*n*	Total[1]	Females (*n* = 14[1])	Males (*n* = 19[1])	*P* value[2]
ALP/RV1c	19	3.72 ± 3.02 (2.86)	2.23 ± 1.58 (1.89)	4.60 ± 3.37 (3.35)	0.045
GGT/RV1c	19	10 ± 9 (5)	5 ± 4 (4)	12 ± 9 (10)	0.210
AST/RV1c	23	5.86 ± 11.29 (3.00)	10.63 ± 18.86 (3.30)	3.31 ± 1.53 (2.86)	0.591
ALT/RV1c	23	3.28 ± 3.19 (2.46)	3.80 ± 5.18 (1.93)	3.01 ± 1.53 (2.75)	0.302
DB	24	7.4 ± 5.3 (5.9)	8.9 ± 5.2 (7.3)	6.8 ± 5.4 (5.9)	0.383
Antibody testing					
ANA	20	3 (15%)	1 (17%)	2 (14%)	> 0.999
AASM	19	2 (11%)	1 (17%)	1 (7.7%)	> 0.999
AMA	19	0 (0%)	0 (0%)	0 (0%)	
ANTI-SLA	11	0 (0%)	0 (0%)	0 (0%)	
pANCA	12	4 (33%)	1 (33%)	3 (33%)	> 0.999
Pre-LTx lab results					
ALT/RV	22	5.5 ± 8.8 (3.0)	6.2 ± 12.6 (2.1)	4.9 ± 4.1 (4.0)	0.138
AST/RV	23	16 ± 44 (5)	24 ± 66	9 ± 14 (5)	0.107
ALP/RV	22	2.79 ± 2.24 (1.84)	2.39 ± 2.37 (1.64)	3.06 ± 2.20 (2.54)	0.393
TB	22	15 ± 10 (11)	13 ± 10 (10)	17 ± 10 (12)	0.324
INR	27	2.08 ± 2.34 (1.51)	1.40 ± 0.32 (1.37)	2.54 ± 2.98 (1.71)	0.025
Creatinine	28	0.89 ± 0.80 (0.75)	0.94 ± 1.19 (0.52)	0.86 ± 0.34 (0.83)	0.143
MELD	27	22.4 ± 6.5 (22.0)	19.9 ± 8.1 (19.0)	24.1 ± 4.7 (23.5)	0.011

[1]Range; mean ± SD (median); *n* (%).
[2]Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test; Pearson's chi-squared test.
AASM: Anti-smooth muscle antibodies; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AMA: Anti-mitochondrial antibody; ANA: Anti-nuclear antibodies; Anti-SLA: Anti-soluble liver antigen; AST: Aspartate transferase; DB: Direct bilirubin; GGT: γ-Glutamyl transferase; INR: International normalized ratio; MELD: Model for end-stage liver disease; pANCA: Perinuclear anti-neutrophil cytoplasmic antibody; RV: Reference value; TB: Total bilirubin; LTx: Liver transplantation.

Table 3 Clinical variables of patients with primary sclerosing cholangitis according to the presence/absence of inflammatory bowel disease

	Total[1]	IBD[1] yes	IBD[1] no	*P* value[2]
Total	26	18 (69.2%)	9 (30.8%)	0.440
Sex				0.692
Male	16 (59%)	6 (67%)	10 (56%)	
Female	11 (41%)	3 (33%)	8 (44%)	
Age	40 ± 13 (36)	38 ± 15 (34)	35 ± 14 (32)	
Ulcerative colitis	15 (83%)			
Crohn's disease	3 (17%)			
AST/RV1c	6.1 ± 12.1 (2.9)	12.2 ± 19.8 (3.7)	2.8 ± 1.6 (2.6)	0.014
DM	5 (19%)	4 (44%)	1 (5.6%)	0.030
Esophageal varices				0.027
No	9 (36%)	0 (0%)	9 (50%)	
Yes	16 (64%)	7 (100%)	9 (50%)	
MELD	21.3 ± 5.5 (22.0)	24.6 ± 5.4 (23.0)	19.3 ± 4.7 (19.0)	0.033
Anastomosis				
Roux-en-Y	8 (31%)	0 (0%)	8 (47%)	0.023
End-to-end	18 (69%)	9 (100%)	9 (53%)	

[1]Range; mean ± SD (median); *n* (%).
[2]Wilcoxon rank sum exact test; Wilcoxon rank sum test; Fisher's exact test; Pearson's χ^2 test.
AST: Aspartate transferase; DM: Diabetes mellitus; MELD: Model for end-stage liver disease; RV: reference value.

and 2 mo) and at 12 years and 6 mo (survival: 18 years).

The overall median post-LTx survival was 66 mo (range: 0–234 mo), with no significant difference between the sexes ($P = 0.282$). Ten deaths occurred, most of which in the first year (infection, $n = 2$; primary liver graft dysfunction, $n = 3$; unknown cause, $n = 1$). Three patients died with coronavirus disease 2019 after 4, 6 and 10 years, respectively, and one patient died of infection 1 year and 7 mo after LTx.

The 1-year and 5-year survival rates of our cohort were 82.3% and 70.6%, respectively. This is compatible with the average overall survival rates of LTx patients at our institution (87.1% and 69.43% respectively) ($P = 0.83$) (Figure 1).

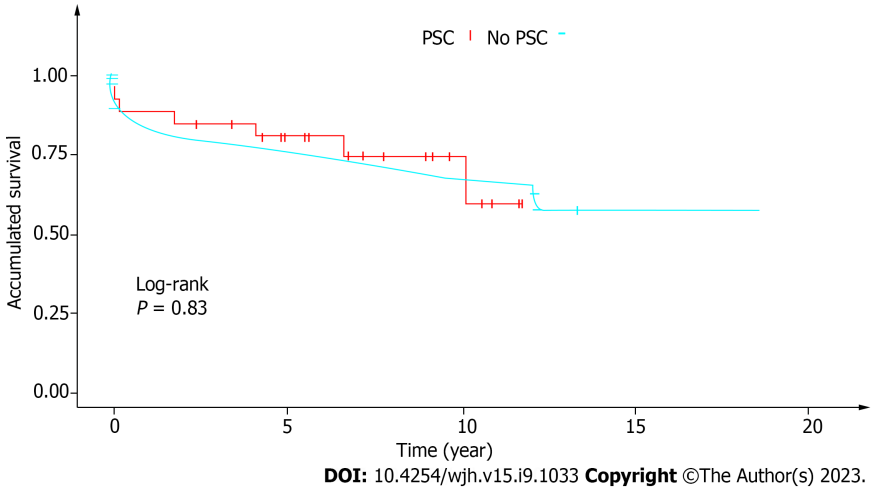
DISCUSSION

PSC represented only 1.6% of all LTx patients in our study, compared with, for example, 15.3% in Nordic countries[6]. The balanced sex distribution in our cohort also differed from that in the international literature, which shows a male predominance (up to 2:1)[7], while matching the proportion observed in a Brazilian multicenter study, in which 45% of the patients were female[8].

The prevalence of classic PSC in our Brazilian cohort matched that of studies from Europe, North America and Australia[9]. The average age of our patients at diagnosis (33 years; range 11–61 years) was similar to that of a Latin American study (29 years; range 19–40 years), but lower than that of a British study (54 years; range 6–93 years)[3,8]. The mean time from the onset of symptoms to diagnosis of PSC was almost twice as long as that in a Swedish study (16 mo) [10].

Elevated serum alkaline phosphatase and γ-glutamyl transferase levels are typical fin PSC patients, but we also observed aspartate aminotransferase and alanine aminotransferase levels on average five and three times above the normal range at the time of diagnosis[11]. According to Williamson and Chapman[12], serum bilirubin levels tend to be normal at disease onset and occasionally fluctuate during the course of the disease. In our cohort, the median bilirubin level was 8.72 mg/dL.

PSC is often associated with IBD[7,13]. PSC may manifest before, concomitantly with, or after the diagnosis of IBD[11]. IBD was observed in 76% of our patients; 67% of whom had concomitant PSC and IDB. The proportion of patients diagnosed with IBD before PSC was similar to that of other studies, as was the predominance of ulcerative rectocolitis[3]. In our cohort, biochemical changes were more pronounced in patients without IBD than in patients with IBD, as was liver disease severity, the occurrence of esophageal varices, and the prevalence of DM, possibly due to the concomitant use of corticoids to treat IBD.



DOI: 10.4254/wjh.v15.i9.1033

Figure 1 Kaplan–Meier survival curve of the general population and patients with primary sclerosing cholangitis. PSC: Primary sclerosing cholangitis.

Current evidence suggests PSC–IBD may be a condition altogether different from PSC alone, and some have argued that PSC may have a protective effect on the course of IBD[12,14], considering the invariably benign course of IBD, with mild or no clinical symptoms and possibly even normal endoscopic appearance observed in PSC patients with a subdiagnosis of IBD. However, concomitant ulcerative rectocolitis increases the risk of colorectal cancer[15].

The presence of a range of autoantibodies in the serum of PSC patients suggests autoimmunity plays a role in pathogenesis, but diagnostic testing for autoantibodies is of limited use due to low sensitivity and specificity[16]. A review on PSC found a high prevalence of p-anti-neutrophil cytoplasmic antibody (50%–80%), anti-nuclear antibody (7%–77%) and anti-mitochondrial autoantibodies (13%–20%)[17], but in our cohort, few patients were tested for antibodies and the prevalence was low.

Most of our patients (93%) were treated with UDCA at least until the time of LTx. UDCA is hepatoprotective in chronic cholestatic liver disease, but its efficacy in PSC has been questioned[18]. In a European study on treatment for PSC[19], 50% of physicians routinely prescribed UDCA for all patients, while 12% never prescribed it. The American Association for the Study of Liver Diseases and the British Society of Gastroenterology do not encourage the use of UDCA in PSC patients[20,21]. The 2009 guidelines of the European Association for the Study of the Liver state that "UDCA (15-20 mg/d) improves serum liver tests and surrogate markers of prognosis (I/B1), but does not reveal a proven benefit on survival (III/C2)"[22].

Lindor *et al*[23] (2009) conducted a double-blind randomized controlled trial on 150 adult PSC patients to evaluate prolonged use of high doses of UDCA (28–30 mg/kg/d). Liver tests did improve, but patients taking UDCA were at higher risk of severe adverse events and clinical outcomes such as cirrhosis, LTx, esophageal varices, CCA and death, when compared with patients receiving placebo. The drug is believed to modify the composition of the bile acids.

Wunsch *et al*[18] (2014) prospectively evaluated the withdrawal of UDCA over 3 mo in 26 PSC patients and found a significant increase in biochemical parameters, nonsignificant deterioration of quality of life in certain domains, and improvement of well-being in the social functioning domain and the mental component summary in SF-36.

Just over half the patients (52%) used prednisone. Immunosuppressants are rarely prescribed for PSC patients and are only indicated in cases of overlap[24].

According to Carey *et al*[4] (2015), up to one fourth of PSC patients submitted to LTx may experience recurrence. In this study, the only patient (3%) with recurrence had concomitant IBD. The association between PSC and IBD is well documented and may affect two thirds of PSC patients, especially when IBD is combined with ulcerative pancolitis[25].

According to Lopens *et al*[24] (2020), patients with concomitant PSC and IBD are at increased risk of liver disease, and the absence of IBD tends to improve the prognosis of PSC and lessen the risk of complications. In contrast, in our study, patients without IBD were not only significantly more severe at the time of LTx but also displayed greater biochemical changes in the early stages of the disease, when compared with patients with concomitant PSC and IBD.

In a large study from the Netherlands involving 3020 PSC patients, the mean time between diagnosis of PSC and indication for LTx was 27 years, compared to 9.7 years in our study[26].

A wide-ranging review by Song *et al*[27] has shown that the risk of CCA is 10 to 1000 times higher in patients with PSC than in the general population. The early diagnosis of CCA in two of our patients agrees with the literature, according to which CCA develops one year after LTx in 50% of cases[27].

In an epidemiological populational study evaluating the risk and malignancy of PSC in 590 patients, the time between diagnosis of PSC and the diagnosis of CCA was on average 6 years, and only 12% were diagnosed with PSC and CCA at the initial presentation. CCA was diagnosed in the first year in 15%, between the first and the tenth year in 37%, and > 10 years later in 37%. The cumulative risk of CCA after 10, 20 and 30 years was 6%, 14% and 20%, respectively[26].

CCA is a formal contraindication for LTx in Brazil. In our cohort, the rate of survival after early recurrence (2 patients) was better than the mean rate given in the literature, according to which the overall survival rate of intrahepatic CCA is 40.8% (39.8%–41.9%) at 1 year, and 9.8% (9%–10.5%) at 5 years[28]. Our 5-year post-LTx survival rate was higher than that

of a British study (75%)[3].

Some caveats apply to this retrospective study: (1) The medical records displayed differences in completeness; (2) PSC and IBD may have been under-reported; and (3) some laboratory findings were inadequately recorded in the database. To obtain the most reliable data possible, primary information was collected from the initial physical, laboratory and image records through active search, while incomplete information and doubts arising from the medical records were addressed by directly contacting the patients by phone.

CONCLUSION

PSC is a rare cause of LTx in our service. In our cohort, the proportion of women was larger than expected. Survival at 1 and 5 years was satisfactory and similar to other LTx indications. CCA findings in explants with good survival rates raise the hypothesis that CCA may be an acceptable indication for LTx in selected cases.

ARTICLE HIGHLIGHTS

Research background

Primary sclerosing cholangitis (PSC) is a rare indication for liver transplantation (LTx). Male sex is predominant in European studies. The ideal moment for LTx can be difficult to determine. PSC is often associated with inflammatory bowel disease (IBD) and may recur after LTx.

Research motivation

A Brazilian multicenter study on PSC showed that LTx patient data are limited and little explored in research. Our LTx service is the largest in North/Northeastern Brazil, with an average of 150 procedures a year, indicating a potential for research. The diagnosis of IBD in PSC patients before and after LTx is often inadequate and requires more attention on part of LTx teams. The finding of associated cholangiocarcinoma (CCA) in explants, associated with good survival, was an additional motivating factor.

Research objectives

To evaluate the clinical profile, complications and survival rates of PSC patients submitted to LTx at a Brazilian referral center.

Research methods

Retrospective study of medical records supplemented by telephone interviews with patients. The study contributed to setting up a database of PSC patients submitted to LTx at our service.

Research results

PSC was observed in 1.6% of LTx patients. Male sex was predominant, but the proportion of women was considerably higher than in the literature. Women were diagnosed later than men, but PSC was more severe in men, including CCA in explants. The prevalence of IBD was 73%. PSC was diagnosed later in IBD patients. The median time from the diagnosis of IBD to the diagnosis of PSC was 9.8 years. Diabetes was significantly more common in patients without IBD. Aspartate transferase was 1.6 times higher in PSC patients with IBD. Esophageal varices were more frequent in non-IBD patients. The most prevalent treatment before LTx was ursodeoxycholic acid. Most men (88%) were treated endoscopically for dominant stenosis prior to LTx. CCA was an incidental finding in two patients with satisfactory survival. The survival of our PSC patients was better than that of LTx patients with other indications at our service. Survival was 81.9% (1 year) and 78.8% (5 years). PSC recurred in 5.88%.

Research conclusions

In our cohort of 34 PSC patients submitted to LTx (2002-2023), the proportion of women was unusually high. CCA patients had satisfactory survival, despite the recurrence of PSC. In patients with both PSC and IBD, the disease was less severe.

Research perspectives

Our study raises the hypothesis that early-stage CCA may be an acceptable indication for LTx. The observed differences in severity in the male sex and the high proportion of women in the cohort require further investigations into the genetic profile of this population.

FOOTNOTES

Author contributions: Freitas LTS and Hyppolito EB designed the study; Freitas LTS, Hyppolito EB, Barreto VL, Júnior LHJC, Jorge BCM,

Háteras FCTSB and Marzola MB reviewed the literature, collected data and drafted the original manuscript; Hyppolito EB performed statistical analyses and reviewed the manuscript; Hyppolito EB, Coelho GR, Garcia JHP, Lima CA and Celedonio RM reviewed the intellectual content of the manuscript; all authors read and approved the final version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the ethics committee of the Federal University of Ceará and filed under Approval No. 98627218.6.2018.5045.

Conflict-of-interest statement: The authors declare they have no conflicts of interest.

Data sharing statement: The dataset available from the corresponding author at louyseteixeira.s@gmail.com.

STROBE statement: The authors declare they have read the STROBE statement. The present manuscript was prepared and revised following the checklist of the STROBE statement.

Country/Territory of origin: Brazil

ORCID number: Louyse Teixeira de Souza Freitas 0000-0003-3274-4808; Elodie Bomfim Hyppolito 0000-0002-6622-6585; Victor Leonardo Barreto 0000-0003-3736-7183; Luiz Humberto Jataí Castelo Júnior 0009-0001-9854-9194; Bianca Carneiro de Melo Jorge 0000-0002-8346-0517; Frederico César Tahim de Sousa Brasil Háteras 0009-0000-2629-069X; Malthus Barbosa Marzola 0009-0007-4619-3003; Clébia Azevedo Lima 0000-0002-7762-7149; Raquel Mendes Celedonio 0009-0000-7155-8464; Gustavo Rêgo Coelho 0000-0003-0845-2864; Jose Huygens Parente Garcia 0000-0003-4401-137X.

S-Editor: Lin C
L-Editor: Kerr C
P-Editor: Cai YX

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World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2023 September 27; 15(9): 1043-1059

DOI: 10.4254/wjh.v15.i9.1043

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Baseline metabolites could predict responders with hepatitis B virus-related liver fibrosis for entecavir or combined with FuzhengHuayu tablet

Yun-Kai Dai, Hai-Na Fan, Kai Huang, Xin Sun, Zhi-Min Zhao, Cheng-Hai Liu

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kao JT, Taiwan; Kishida Y, Japan

Received: June 8, 2023
Peer-review started: June 8, 2023
First decision: August 5, 2023
Revised: August 21, 2023
Accepted: September 14, 2023
Article in press: September 14, 2023
Published online: September 27, 2023

Yun-Kai Dai, Hai-Na Fan, Xin Sun, Zhi-Min Zhao, Cheng-Hai Liu, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Institute of Liver Diseases, Shanghai 201203, China

Kai Huang, Xin Sun, Zhi-Min Zhao, Cheng-Hai Liu, Shanghai Key Laboratory of Traditional Chinese Clinical Medicine, Institute of Liver Diseases, Shanghai 201203, China

Cheng-Hai Liu, Key Laboratory of Liver and Kidney Diseases, Institute of Liver Diseases, Shanghai 201203, China

Corresponding author: Cheng-Hai Liu, MD, PhD, Director, Doctor, Professor, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Institute of Liver Diseases, No. 528 Zhangheng Road, Pudong New Area, Shanghai 201203, China.
chenghai.liu@shutcm.edu.cn

Abstract

BACKGROUND

After receiving entecavir or combined with FuzhengHuayu tablet (FZHY) treatment, some sufferers with hepatitis B virus (HBV)-related liver fibrosis could achieve a histological improvement while the others may fail to improve even worsen. Serum metabolomics at baseline in these patients who were effective in treatment remain unclear.

AIM

To explore baseline serum metabolites characteristics in responders.

METHODS

A total of 132 patients with HBV-related liver fibrosis and 18 volunteers as healthy controls were recruited. First, all subjects were divided into training set and validation set. Second, the included patients were subdivided into entecavir responders (E-R), entecavir no-responders (E-N), FZHY + entecavir responders (F-R), and FZHY + entecavir no-responders (F-N) following the pathological histological changes after 48 wk' treatments. Then, Serum samples of all subjects before treatment were tested by high performance liquid chromatography-tandem mass spectrometry (LC-MS) high-performance LC-MS. Data processing was conducted using multivariate principal component analysis and orthogonal

partial least squares discriminant analysis. Diagnostic tests of selected differential metabolites were used for Boruta analyses and logistic regression.

RESULTS

As for the intersection about differential metabolic pathways between the groups E-R *vs* E-N and F-R *vs* F-N, results showed that 4 pathways including linoleic acid metabolism, aminoacyl-tRNA biosynthesis, cyanoamino acid metabolism, alanine, aspartate and glutamate metabolism were screened out. As for the differential metabolites, these 7 intersected metabolites including hydroxypropionic acid, tyrosine, citric acid, taurochenodeoxycholic acid, benzoic acid, 2-Furoic acid, and propionic acid were selected.

CONCLUSION

Our findings showed that 4 metabolic pathways and 7 differential metabolites had potential usefulness in clinical prediction of the response of entecavir or combined with FZHY on HBV fibrotic liver.

Key Words: Serum metabolomics; Differential metabolites; Therapeutic responders; Entecavir; FuzhengHuayu tablet; Hepatitis B virus-related liver fibrosis

Core Tip: This study will use high-performance liquid chromatography-tandem mass spectrometry and multivariate statistical modelings to predict serum metabolites of the treatment (entecavir or entecavir + FuzhengHuayu tablet) that effectively reversed hepatitis B virus-related liver fibrosis. It is of great theoretical and practical significance to prevent the transformation of liver fibrosis to cirrhosis or even hepatocellular carcinoma and reduce the social burden.

Citation: Dai YK, Fan HN, Huang K, Sun X, Zhao ZM, Liu CH. Baseline metabolites could predict responders with hepatitis B virus-related liver fibrosis for entecavir or combined with FuzhengHuayu tablet. *World J Hepatol* 2023; 15(9): 1043-1059
URL: https://www.wjgnet.com/1948-5182/full/v15/i9/1043.htm
DOI: https://dx.doi.org/10.4254/wjh.v15.i9.1043

INTRODUCTION

Liver fibrosis, characterized by the progressive and reversible accumulation of fibrillar extracellular matrix components in the liver, poses a significant threat to the physiological architecture of the liver and accounts for nearly half of all-cause mortality associated with various liver diseases worldwide[1-2]. Among the numerous causes of acute and chronic liver diseases, hepatitis B virus (HBV) infection stands out as a prevalent culprit and a leading instigator of liver fibrosis[3]. Epidemiological studies have revealed that more than 240 million individuals are afflicted by HBV infection[4]. Given the insidious nature of chronic hepatitis B (CHB), it can swiftly advance to fibrosis, cirrhosis, or even hepatocellular carcinoma (HCC) if left unchecked[5]. Hence, it is imperative to consider the use of antiviral agents in the treatment of HBV, with entecavir serving as a prominent representative.

In recent years, the study of liver fibrosis has consistently been a focal point of medical research[6]. Serving as a reversible lesion, liver fibrosis acts as the intermediary stage between the development of chronic liver diseases and the progression to cirrhosis[7]. Presently, effective treatments for cirrhosis remain limited, underscoring the significance of anti-liver fibrosis as a crucial therapeutic strategy. FuzhengHuayu tablet (FZHY), a novel traditional Chinese medicine (TCM) remedy, has gained widespread usage in clinical practice for the treatment of liver fibrosis and cirrhosis[8]. Furthermore, our prior multi-center clinical investigation has substantiated that entecavir + FZHY therapy significantly enhances the histological reversal rate of CHB fibrosis[9]. Nonetheless, approximately one-third of patients fail to exhibit a substantial histological response[10]. Consequently, elucidating the biological characteristics of individuals who respond to entecavir or entecavir + FZHY will undoubtedly contribute to the enhancement of precision therapy's therapeutic efficacy.

To date, no single biomarker or scoring system has achieved the ideal balance of sensitivity and specificity for the detection and characterization of liver fibrosis[11]. While liver biopsy remains the gold standard for staging liver fibrosis, it is burdened by limitations such as invasiveness, sampling errors, and the potential for complications[12]. Furthermore, this method lacks convenience in tracking the dynamic progression of liver fibrosis and assessing therapeutic outcomes. Fortunately, non-invasive diagnostic techniques for liver fibrosis, including transient elastography (Fibroscan), elastography, and diffusion-weighted magnetic resonance imaging, have made significant advancements and gained widespread clinical utility. However, these approaches are susceptible to interference from factors such as a patient's body mass index (BMI), liver inflammation, or hepatocyte degeneration[13].

Metabolomics, an emerging field following in the footsteps of genomics, transcriptomics, and proteomics, represents a novel approach to systematically study changes in small-molecule metabolites produced by the body's metabolism[14]. Often referred to as the "end point" of the genome and proteome, metabolomics allows for the comprehensive analysis of

various metabolites and their metabolic pathways in a population, offering high-throughput and modeling capabilities. Furthermore, metabolomics can unveil downstream products of gene and protein expression within an organism, providing insight into all physiological processes within the body. Due to its close proximity to disease phenotypes, metabolomics is particularly well-suited for disease classification and biomarker discovery. In this study, we intend to employ high-performance liquid chromatography-mass spectrometry (HPLC-MS) and advanced multivariate statistical modeling to predict serum metabolite profiles associated with the effective reversal of HBV-related liver fibrosis induced by treatment with entecavir or entecavir + FZHY. This research holds profound theoretical and practical significance in preventing the progression of liver fibrosis to cirrhosis or HCC, thereby reducing the societal burden associated with these conditions.

MATERIALS AND METHODS

Patient selection

This is a cross-sectional study that encompasses multi-center randomized controlled clinical trials. We enrolled a total of 132 patients with HBV-related liver fibrosis, along with 18 healthy volunteers as controls, during the period from September 9, 2014, to October 25, 2018. The study comprised two distinct sets: A training set and a validation set. All participants were recruited from 20 hospitals across China and provided voluntary informed consent. The research protocol received ethical approval from the Ethics Committee of Shuguang Hospital Affiliated with Shanghai University of TCM (ethical approval number: 2014-331-27-01). The diagnostic criteria for HBV-related liver fibrosis were in accordance with the guidelines for the prevention and treatment of CHB (2019)[15]. The primary focus of this study was on the progression of liver fibrosis, assessed primarily through liver histopathology using the Ishak scoring system as the indicator for therapeutic evaluation. The primary outcome measured was the proportion of patients demonstrating a 1-point improvement in liver fibrosis stage, as per the Ishak score, from baseline to 48 wk. Liver biopsies were performed both before and 48 wk after the initiation of combination TCM treatment, and the histopathological evaluation was independently conducted by three pathologists. Fibrosis regression was defined as a decrease in the Ishak score of 1 or greater[16]. The final fibrotic scores were established based on consensus among two or more pathologists; any disagreements were resolved by a central pathologist. However, a detailed assessment of inflammation levels was not performed. For the noninvasive diagnosis and staging of liver fibrosis, aminotransferase-to-platelet ratio index (APRI) and fibrosis index based on the 4 factor (FIB-4) were primarily employed as adjunct diagnostic tools to assess the severity of liver fibrosis. Consequently, the two treatment groups were further subdivided into four subgroups: Entecavir responders (E-R), entecavir non-responders (E-N), FZHY + entecavir responders (F-R), and FZHY + entecavir non-responders (F-N). Inclusion criteria for this study encompassed individuals aged 18 years or older who met the aforementioned diagnostic criteria. Exclusion criteria included the following: individuals with liver fibrosis not associated with HBV infection; those with cardio-cerebrovascular or infectious diseases or other digestive system disorders; pregnant or lactating women; and patients with poor compliance.

Sample collection

All subjects were asked to have normal regular diets and schedules on the day before blood collection, and venous blood was collected on an empty stomach the next morning. 500 μL serum was centrifuged at 4 ℃ at 4000 r/min and stored in a -80 ℃ for later use.

Sample processing

The cryopreserved serum was thawed on ice-bath in case of degradation. 25 μL of serum was added to a 96-well plate for the transferring to the Biomek 4000 workstation (Biomek 4000, Beckman Coulter, Inc., Brea, CA, United States). 120 μL of methanol was automatically added to each serum and vortexed for 5 min. The plate was centrifuged at 4000 g for half an hour and it was returned back to the workstation. 30 μL of supernatant fluid was transferred to a clean 96-well plate, where each well was filled with 20 μL of freshly prepared derivative reagents. Then the plate was sealed for derivatization at 30 ℃ for an hour and the sample was diluted by 330 μL of ice-cold 50% methanol solution. Next, the plate was left at -20 ℃ for 20 min and centrifuged at 4 ℃ for half an hour. Finally, 135 μL of supernatant fluid was taken to a new 96-well plate, which was sealed for liquid chromatography-tandem mass spectrometry (LC-MS) analysis.

Quality control analysis

All samples were mixed into one quality control sample for quality control. The quality control samples were analyzed 6 times and randomly respectively tested 2 times before, during and after analysis. The total ion flow chromatograms of the quality control samples were overlapped and the total principal component analysis (PCA) was performed. It would show good repeatability if the results of the quality control samples were close to each other.

Materials and reagents

Formic acid (Optima grade) was obtained from Sigma-Aldrich (St. Louis, MO, United States). Methanol (Optima LC-MS) and acetonitrile (Optima LC-MS) were purchased from Thermo-Fisher Scientific (FairLawn, NJ, United States). The experimental water was distilled water.

Instrument analysis platform

We used a ultra-performance liquid chromatography coupled to tandem mass spectrometry system (ACQUITY UPLC-Xevo TQ-S, Waters Corp., Milford, MA, United States) in order to quantitate all targeted metabolites in this study. A briefly description of the optimized instrument settings can be shown in Supplementary Table 1. Meanwhile, the instrument performance optimization and routine maintenance were conducted every week.

LC-MS analysis

Extraction of ion flow chromatograms based on HPLC-MS. (1) Chromatographic elution gradient: The initial gradients were 5% solution B (acetonitrile + 0.1% formic acid) and 95% solution A (distilled water + 0.1% formic acid), whose elution time lasted 2-10 min. Meanwhile, solution B increased linearly to 95% for 5 min and then dropped back to 5%. The injection volume was 4 uL and the automatic sampler temperature was 4 ℃; and (2) mass spectrometry scanning mode: Positive and negative ions were used for detection by mass spectrometry. The ion scanning time was 0.03 s, the time interval was 0.02 s, and the data collection range was 50-100 m/z.

Screening and identification of potential metabolites

The data of group A and group B were analyzed by total PCA, then partial least squares discriminant analysis (PLS-DA) was used, and finally the supervised orthogonal PLS-DA (OPLS-DA) was used for modeling analysis. Variable importance in the projection (VIP) values (threshold > 1) based on the OPLS-DA model, combined with P value ($P < 0.05$) of t test, were used to find metabolites which were differentially expressed. Potential metabolites were identified by searching online database (http://metlin.scripps.edu/) to compare the mass charge ratio or molecular mass of mass spectrometry.

Potential metabolite enrichment analysis and metabolic pathway analysis

Metabo-Analyst online analysis software (https://www.metaboanalyst.ca) and Kyoto Encyclopedia of Genes and Genomes databases (https://www.kegg.jp/) were used for metabolic pathway analysis and enrichment analysis of the identified potential metabolites so as to determine the metabolic pathways involved in the potential metabolites, and to evaluate the diagnostic performance of the potential metabolites enriched in pathways.

Diagnostic tests

In order to validate the applicability and stability of the selected differential metabolites, random forest (RF), Support vector machine (SVM) and Boruta analyses were conducted for each selected metabolite in sequence. Boruta analysis, the maximum number of runs with 1000, was an RF-based feature selection method that it selects key features with more significant distinguishing ability than random lag features. When provisional features were included, a secondary selection was made to determine whether certain metabolites with large fluctuations should be included in the selected features.

These differential metabolites used for subsequent model construction were modeled and predicted using logistic regression. After modeling, sensitivity and specificity values were calculated to evaluate the model effects through drawing the receiver operating characteristic curve. Meanwhile, the closer the area under the curve (AUC) value is to 1, the better the sensitivity, specificity and diagnostic abilities. The conventional AUC of metabolites with the value ≥ 0.75 indicated relatively good sensitivity and specificity.

Statistical analysis

Statistical analysis software packages in R studio (http://cran.r-project.org/) were performed for the statistical algorithms. All the included data were calculate with mean ± SD or median-interquartile range. The Mann-Whitney U test or t test was used for the statistical differences in pairwise comparison. Multivariate statistical modelings including PCA, PLS-DA, and OPLS-DA were used for the multi-class classification and identification of differently altered metabolites. Among these modelings, each spatial dot in the K-dimensional space represented an individual sample with the samples color-coded based on grouping information. R^2X and R^2Y respectively represented the fraction of the variance of X matrix and Y matrix, while Q^2Y represented the predictive accuracy of the model. Cumulative values of R^2X and R^2Y approaching 1.0, along with Q^2Y greater than 0.2 (permutation test), indicated a model with a satisfactory predictive ability. Those variables with VIP greater than 1.0 are considered significantly different between classes. If multidimensional statistics cannot establish a robust discriminant model (such as uneven distribution of inter-group sample categories or large intra-group deviation), differential metabolites between the two groups would be acquired with the aid of univariate analysis.

RESULTS

Baseline clinical characteristics of participants

In the training set, there were 23 sufferers in each subgroup and 13 normal volunteers as control. In the validation set, there were 10 patients in each subgroup and 5 volunteers as control. Details of the baseline clinical characteristics of the two datasets can be found in Table 1. Specifically, there were no significant differences in the gender, age, BMI, alanine aminotransferase, aspartate aminotransferase, albumin (ALB), total bilirubin (TBIL), creatinine, prothrombin time, platelet count, alpha fetoprotein, FIB-4, aspartate APRI, Ishak score in the training set ($P > 0.05$). However, in the

Table 1 Demographic and clinical data of patients and volunteers in training set and validation set

	Training set (*n* = 105)					Validation set (*n* = 45)				
	F-R (*n* = 23)	F-N (*n* = 23)	E-R (*n* = 23)	E-N (*n* = 23)	NOR (*n* = 13)	F-R (*n* = 10)	F-N (*n* = 10)	E-R (*n* = 10)	E-N (*n* = 10)	NOR (*n* = 5)
Male/Female	15/8	15/8	16/7	17/6	9/4	7/3	10/0	6/4	8/2	4/1
Age (yr)	44.17 ± 6.25	42.43 ± 8.36	40.65 ± 7.73	42.22 ± 7.97	36.92 ± 6.18	42.80 ± 5.01	38.10 ± 11.95	45.00 ± 7.93	47.40 ± 10.44	37.80 ± 8.79
BMI (kg/m^2)	23.60 ± 2.56	23.64 ± 3.17	23.54 ± 2.06	23.92 ± 2.73	24.20 ± 1.34	23.22 ± 3.30	24.76 ± 1.65	24.61 ± 2.29	23.16 ± 3.86	22.60 ± 1.71
ALT (IU/L)	42.52 ± 29.59	41.03 ± 20.48	68.91 ± 89.81	47.34 ± 27.83	/	49.80 ± 50.83	48.80 ± 33.14	57.08 ± 46.97	58.33 ± 73.02	/
AST (IU/L)	40.50 ± 21.35	41.80 ± 19.41	53.47 ± 51.20	50.53 ± 27.59	/	38.71 ± 16.39	47.75 ± 28.32	77.64 ± 120.70	48.73 ± 35.54	/
ALB (IU/L)	43.84 ± 5.50	41.43 ± 6.07	43.51 ± 5.75	42.22 ± 4.61	/	42.40 ± 5.08	35.70 ± 6.67	39.68 ± 5.95	41.53 ± 4.64	/
TBIL (μmol/L)	16.15 ± 10.88	13.27 ± 6.36	13.36 ± 9.25	14.16 ± 6.51	/	11.98 ± 4.90	24.49 ± 16.83	22.08 ± 13.61	12.18 ± 5.79	/
Cr (μmol/L)	64.43 ± 17.03	66.39 ± 11.99	69.57 ± 16.59	64.57 ± 14.67	/	72.80 ± 18.27	71.10 ± 9.71	65.80 ± 13.70	83.60 ± 25.07	/
PT (S)	13.22 ± 1.48	13.23 ± 1.41	13.31 ± 1.46	13.78 ± 1.52	/	13.21 ± 1.32	14.27 ± 2.90	14.10 ± 1.33	13.88 ± 1.83	/
PLT (× 10 ×^{9}/L)	119.02 ± 49.99	113.47 ± 61.33	131.70 ± 49.26	104.65 ± 41.65	/	145.10 ± 64.42	112.00 ± 36.18	98.88 ± 45.13	106.40 ± 37.97	/
AFP (ng/ml)	23.70 ± 59.55	12.46 ± 13.22	18.63 ± 42.03	14.75 ± 15.56	/	16.73 ± 31.93	54.81 ± 93.15	25.25 ± 41.79	14.86 ± 15.91	/
FIB-4	2.99 ± 2.06	3.31 ± 2.38	2.54 ± 1.62	3.46 ± 1.75	/	2.29 ± 1.95	2.72 ± 1.51	5.63 ± 8.14	3.55 ± 1.89	/
APRI	1.10 ± 0.96	1.23 ± 0.95	1.40 ± 1.60	1.31 ± 0.73	/	0.81 ± 0.54	1.18 ± 0.84	3.17 ± 6.23	1.28 ± 0.92	/
Ishak score	5.48 ± 0.51	5.43 ± 0.51	5.35 ± 0.49	5.39 ± 0.50	/	5.40 ± 0.52	5.40 ± 0.52	5.50 ± 0.53	5.10 ± 0.32	/

BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALB: Albumin; TBIL: Total bilirubin; Cr: Creatinine; PT: Prothrombin time; PLT: Platelet count; AFP: Alpha fetoprotein; FIB-4: Fibrosis index based on the 4 factor; APRI: Aspartate aminotransferase-to-platelet ratio index; E-R: Entecavir responders; E-N: Entecavir no-responders; F-R: FuzhengHuayu tablet + entecavir responders; F-N: FuzhengHuayu tablet + entecavir no-responders; NOR: Normal.

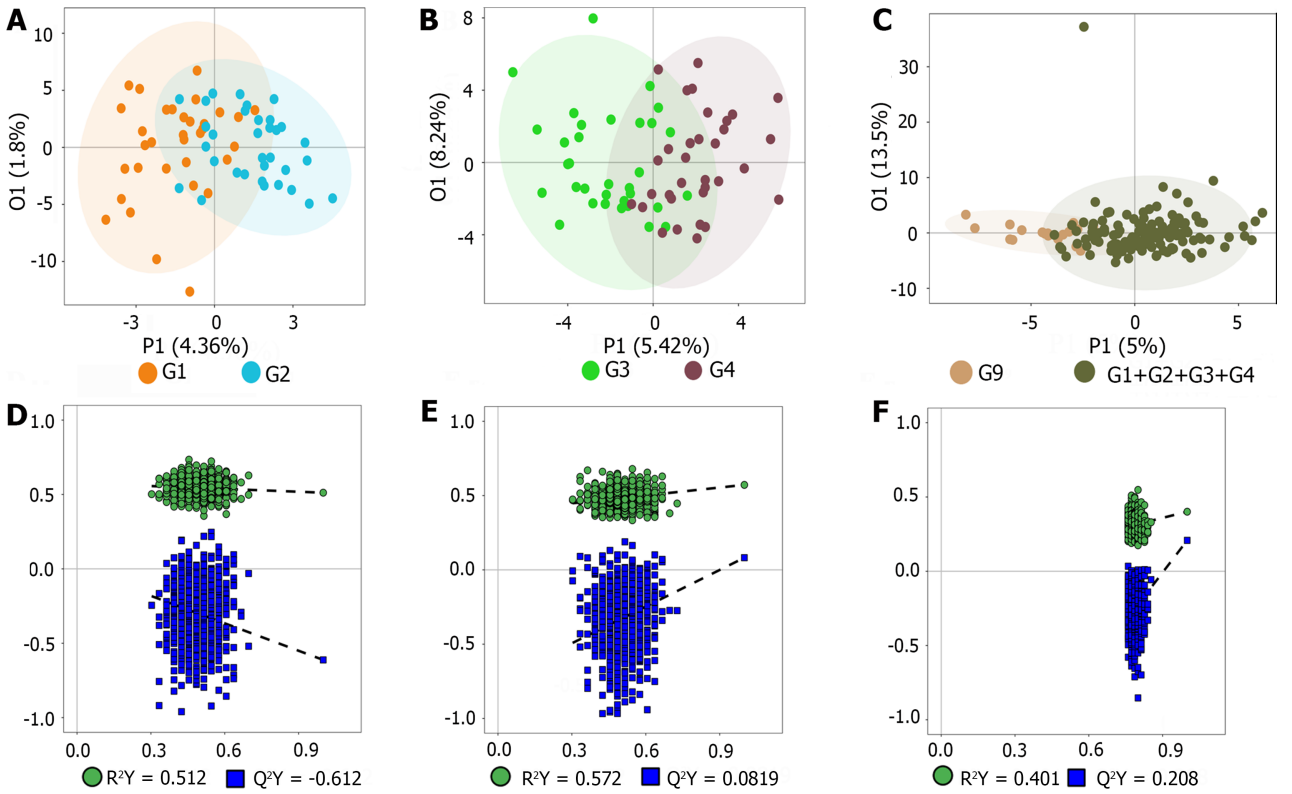
validation set, the serum ALB and TBIL levels significantly differed between the F-R and F-N patients ($P < 0.05$), but the other indexes were not statistically significant ($P > 0.05$).

The pathological histological results of the liver biopsy

The obtained tissues *via* liver biopsy were fixed in 10% formalin and embedded in paraffin. Sections of each liver tissue were cut and stained using hematoxylin-eosin (HE) staining for histopathological analysis. Based on the HE staining results and Ishak score, staging of liver fibrosis was determined as F1 to F6[17]. Briefly, F1: Some portal areas have fibrosis but no fibrous septum; F2: Many portal areas have fibrosis along with one fibrous septum; F3: Many portal areas have fibrosis along with two or three fibrous septa; F4: Portal areas have obvious portal-junction bridge fibrosis along with more than four fibrous septa; F5: Portal areas have obvious portal-junction bridge fibrosis or portal-central bridge fibrosis along with one to three pseudolobuli and F6: More than three pseudolobuli. Details of relevant figures can be found in Supplementary Figure 1.

Overall metabolomics analysis of serum samples

Representative nuclear magnetic resonance spectra with targeted metabolites are exhibited in Supplementary Figure 2. The serum spectra included high-intensity signals from Maleic acid, Glycine (G1 *vs* G2), dihomo-gamma-linolenic acid, arachidonic acid, hydroxypropionic acid, (G3 *vs* G4), 2-Furoic acid, 2-Phenylpropionate, arachidonic acid, benzoic acid, butyric acid, aconitic acid, citric acid, dimethylglycine, glycochenodeoxycholic acid (GCDCA), homovanillic acid, hydrocinnamic acid, hydroxyphenyllactic acid, isocitric acid, tyrosine, phenyllactic acid, propionic acid, taurochenodeoxycholic acid (TCDCA), tricarboxylic acid (TCA) (G9 *vs* G1-G4). Because all patients were suffered from HBV-related



DOI: 10.4254/wjh.v15.i9.1043

Figure 1 Orthogonal partial least squares discriminant analysis of all the metabolites. A: Score of entecavir responders (E-R) *vs* entecavir no-responders (E-N); B: Score of FuzhengHuayu tablet (FZHY) + entecavir responders (F-R) *vs* FZHY + entecavir no-responders (F-N); C: Score of patients vs volunteers; D: R^2X and R^2Y of E-R vs E-N; E: R^2X and R^2Y of F-R vs F-N; F: R^2X and R^2Y of patients vs volunteers.

liver fibrosis in this study, statistical assessment by PCA indicated not clear separation in each group (E-R *vs* E-N; F-R *vs* F-N; patients vs volunteers) (Supplementary Figure 3). Besides, in order to exclude the possible confounding factors irrelevant to the group differences and to assess the statistical meaning of those signals, OPLS-DA was conducted and the result showed that the discrimination model could differentiate the two groups despite within a small overlap in one orthogonal component (Figure 1A-C). Moreover, as shown in Figure 1D-F, the models with $R^2(Y)$ of 0.512 (E-R *vs* E-N), 0.572 (F-R *vs* F-N), 0.401 (patients *vs* volunteers) suggested relatively good predictability and no potential over-fit. However, the models with $Q^2(Y)$ of -0.612 (E-R *vs* E-N), 0.0819 (F-R *vs* F-N), and 0.208 (patients *vs* volunteers) indicated the potential risk of over-fit.

Serum metabolites relevant to responders and HBV-related liver fibrosis

Due to the possibility of potential risk of the over-fit in these models, differential metabolites between the two groups were acquired with the aid of univariate analysis instead of analysis together with the VIP values from the above OPLS-DA model. Furthermore, in order to explore the applicability and stability of the distinctive models, serum samples from all the included patients and volunteers were collected and analyzed using the training set and validation set for the subsequent analyses.

In order to find out potential metabolites involving in responders and HBV-related liver fibrosis among the thousands of variables, a pairwise comparison in each group was conducted. According to the threshold value ($P < 0.05$ and $|\log2FC| \geq 0$, FC: Fold change), a total of 2 (E-R *vs* E-N), 16 (F-R *vs* F-N) and 35 (patients *vs* volunteers) potential metabolites in the training set (Figure 2A-C) were obtained while a total of 8 (E-R *vs* E-N), 7 (F-R *vs* F-N) and 23 (patients *vs* volunteers) potential metabolites in the validation set (Figure 2D-F) were acquired.

Selection of potential metabolites in different sets

By taking intersection and union set in terms of the aforementioned obtained unidimensional and multidimensional potential metabolites, these metabolites that may have biological significance can be selected on the basis of OPLS-DA (VIP > 1) and univariate ($P < 0.05$ and $|\log2FC| \geq 0$) analyses. A total of 53 potential metabolites in the training set and 38 potential metabolites in the validation set were obtained. Detailed information of these selected potential metabolites were shown in Table 2. The distribution of data for all the metabolites in each group can be found in Supplementary Figure 4. Furthermore, a heat map, together with Z-score, was used for analysis of these selected metabolites and the results suggested that the pairwise comparisons between the two groups could be separated no matter which data set was (Figure 3).

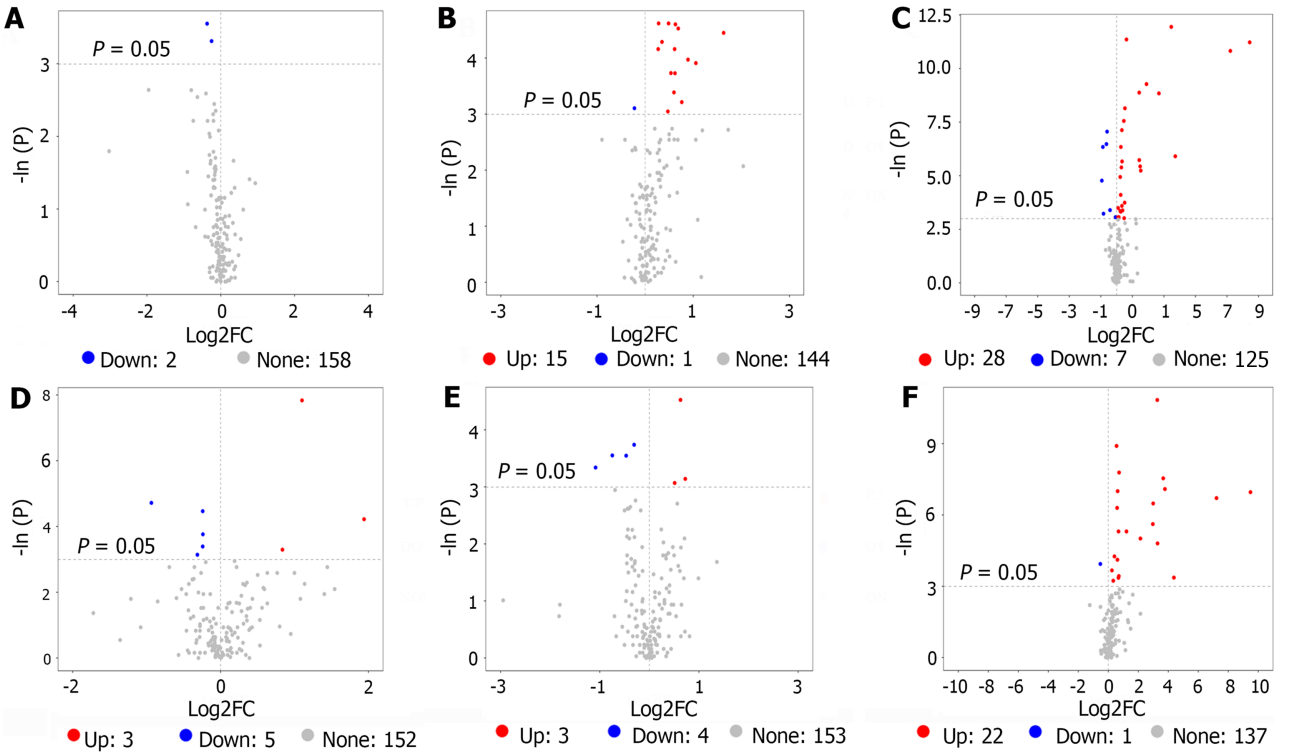
Table 2 The selected potential metabolites in training set and validation set

Class	HMDB	KEGG	Metabolite	Uni_P	Uni_FDR	FC	log2FC	OPLSDA_VIP
Training set								
Fatty acids	HMDB0000448	C06104	Adipic acid	0.03	1.00	0.77	-0.37	1.65
Organic acids	HMDB0000176	C01384	Maleic acid	0.04	1.00	0.84	-0.25	1.73
Fatty acids	HMDB0060038	NA	10Z-Heptadecenoic acid	0.01	0.31	3.10	1.63	1.90
	HMDB0002925	C03242	Dihomo-gamma-linolenic acid	0.02	0.32	2.08	1.05	1.60
	HMDB0001043	C00219	Arachidonic acid	0.04	0.44	1.70	0.76	1.79
	HMDB0002183	C06429	DHA	0.02	0.32	1.85	0.89	2.03
	HMDB0006528	C16513	DPA	0.01	0.31	1.55	0.63	1.99
	HMDB0001999	C06428	EPA	0.02	0.32	1.54	0.62	1.70
Organic acids	HMDB0000700	C01013	Hydroxypropionic acid	0.01	0.31	1.27	0.35	1.21
Fatty acids	HMDB0000673	C01595	Linoleic acid	0.05	0.44	1.39	0.47	1.54
Carnitines	HMDB0006469	NA	Linoleylcarnitine	0.01	0.31	1.40	0.49	2.16
Fatty acids	HMDB0000806	C06424	Myristic acid	0.01	0.31	1.61	0.69	1.76
	HMDB0000207	C00712	Oleic acid	0.02	0.32	1.45	0.54	1.86
Carnitines	HMDB0005065	NA	Oleylcarnitine	0.01	0.31	1.21	0.28	2.32
Fatty acids	HMDB0003229	C08362	Palmitoleic acid	0.02	0.31	1.53	0.61	1.62
	HMDB0000826	C16537	Pentadecanoic acid	0.03	0.42	1.51	0.60	1.51
Benzenoids	HMDB0000205	C00166	Phenylpyruvic acid	0.04	0.44	0.86	-0.22	0.85
Carnitines	HMDB0013128	NA	Valerylcarnitine	0.02	0.31	1.21	0.27	1.47
Organic acids	HMDB0000617	C01546	2-Furoic acid	0.00	0.00	148.12	7.21	2.10
Phenylpropanoic acids	HMDB0011743	NA	2-Phenylpropionate	0.01	0.04	2.89	1.53	1.26
Organic acids	HMDB0000357	C01089	3-Hydroxybutyric acid	0.04	0.20	0.56	-0.83	0.59
Fatty acids	HMDB0000555	NA	3-Methyladipic acid	0.05	0.22	0.95	-0.07	2.09
	HMDB0001043	C00219	Arachidonic acid	0.00	0.01	0.66	-0.60	2.11
	HMDB0000784	C08261	Azelaic acid	0.05	0.22	1.07	0.10	0.86
Organic acids	HMDB0001870	C00180	Benzoic acid	0.00	0.00	346.31	8.44	2.42
Bile acids	HMDB0000686	C17662	bUDCA	0.00	0.02	0.64	-0.64	1.37
SCFAs	HMDB0000039	C00246	Butyric acid	0.00	0.00	3.72	1.89	2.54
Carnitines	HMDB0002013	C02862	Butyrylcarnitine	0.00	0.02	0.55	-0.87	1.80
Bile acids	HMDB0000619	C00695	CA	0.02	0.16	1.42	0.51	1.27
Organic acids	HMDB0000072	C02341	Aconitic acid	0.00	0.01	1.37	0.46	0.76
	HMDB0000094	C00158	Citric acid	0.00	0.02	1.21	0.27	1.31
Carbohydrates	HMDB0000122	C00221	Glucose	0.05	0.22	1.10	0.14	0.75
Carnitines	HMDB0000651	NA	Decanoylcarnitine	0.01	0.06	0.52	-0.94	0.55
Amino acids	HMDB0000092	C01026	Dimethylglycine	0.00	0.03	1.27	0.35	0.90
Amino acids	HMDB0000112	C00334	GABA	0.01	0.05	1.17	0.23	0.46
	HMDB0000123	C00037	Glycine	0.04	0.19	1.18	0.23	1.07
Bile acids	HMDB0000637	C05466	GCDCA	0.00	0.00	6.42	2.68	2.30
Organic acids	HMDB0000115	C00160	Glycolic acid	0.03	0.18	1.26	0.33	1.03
Fatty acids	HMDB0000666	C17714	Heptanoic acid	0.03	0.19	1.30	0.38	1.07

Phenols	HMDB0000118	C05582	Homovanillic acid	0.00	0.01	1.26	0.33	2.40
Phenylpropanoic acids	HMDB0000764	C05629	Hydrocinnamic acid	0.00	0.03	2.71	1.44	1.23
	HMDB0000755	C03672	Hydroxyphenyllactic acid	0.00	0.01	1.44	0.53	2.20
Organic acids	HMDB0000193	C00311	Isocitric acid	0.05	0.22	1.39	0.48	0.65
	HMDB0000168	C00152	Asparagine	0.03	0.19	1.07	0.10	1.85
	HMDB0000719	C00263	Homoserine	0.04	0.19	1.20	0.26	1.41
	HMDB0000696	C00073	Methionine	0.00	0.04	1.23	0.30	1.59
	HMDB0000716	C00408	Pipecolic acid	0.02	0.11	1.20	0.26	0.98
	HMDB0000158	C00082	Tyrosine	0.00	0.00	1.54	0.62	2.51
Carnitines	HMDB0000791	C02838	Octanoylcarnitine	0.03	0.19	0.75	-0.42	0.57
Phenylpropanoic acids	HMDB0000779	NA	Phenyllactic acid	0.00	0.04	2.81	1.49	1.44
SCFAs	HMDB0000237	C00163	Propionic acid	0.00	0.00	2.70	1.43	3.00
Bile Acids	HMDB0000951	C05465	TCDCA	0.00	0.00	11.04	3.47	1.80
	HMDB0000036	C05122	TCA	0.00	0.03	13.19	3.72	1.55
Validation set								
Carnitines	HMDB0000062	C00318	Carnitine	0.04	0.65	0.80	-0.31	1.73
	HMDB0001976	NA	DPAn-6	0.04	0.65	1.79	0.84	2.00
	HMDB0003073	C06426	gamma-Linolenic acid	0.01	0.59	3.84	1.94	2.54
Amino acids	HMDB0000123	C00037	Glycine	0.03	0.65	0.85	-0.24	1.60
Peptides	HMDB0000721	NA	Glycylproline	0.01	0.59	0.85	-0.24	1.59
Amino acids	HMDB0000168	C00152	Asparagine	0.02	0.65	0.85	-0.24	1.41
	HMDB0000162	C00148	Proline	0.01	0.59	0.52	-0.94	1.53
	HMDB0006270	NA	Linoelaidic acid	0.00	0.06	2.15	1.10	2.62
	HMDB0002925	C03242	Dihomo-gamma-linolenic acid	0.04	0.80	1.65	0.72	1.39
	HMDB0001043	C00219	Arachidonic acid	0.05	0.80	1.42	0.51	1.59
Organic acids	HMDB0000700	C01013	Hydroxypropionic acid	0.04	0.80	0.47	-1.08	2.07
Amino acids	HMDB0000168	C00152	Asparagine	0.02	0.80	0.81	-0.31	2.66
	HMDB0000191	C00049	Aspartic acid	0.01	0.80	1.55	0.63	2.29
	HMDB0000158	C00082	Tyrosine	0.03	0.80	0.72	-0.47	2.51
Phenylpropanoic acids	HMDB0000779	NA	Phenyllactic acid	0.03	0.80	0.60	-0.75	2.14
Organic acids	HMDB0000617	C01546	2-Furoic acid	0.00	0.02	148.81	7.22	1.66
Phenylpropanoic acids	HMDB0011743	NA	2-Phenylpropionate	0.00	0.02	13.73	3.78	1.90
Fatty acids	HMDB0001043	C00219	Arachidonic acid	0.02	0.17	0.69	-0.53	1.88
Organic acids	HMDB0001870	C00180	Benzoic acid	0.00	0.02	715.57	9.48	1.71
SCFAs	HMDB0000039	C00246	Butyric acid	0.00	0.05	7.84	2.97	1.80
	HMDB0000072	C02341	Aconitic acid	0.00	0.06	1.60	0.68	1.90
	HMDB0000094	C00158	Citric acid	0.00	0.02	1.54	0.62	2.32
Amino acids	HMDB0000092	C01026	Dimethylglycine	0.00	0.02	1.65	0.72	0.97
Bile acids	HMDB0000637	C05466	GCDCA	0.00	0.02	12.69	3.67	1.53
Phenols	HMDB0000118	C05582	Homovanillic acid	0.00	0.03	1.51	0.59	2.32
	HMDB0000764	C05629	Hydrocinnamic acid	0.00	0.03	7.97	2.99	1.88

	HMDB0000755	C03672	Hydroxyphenyllactic acid	0.03	0.25	1.63	0.70	2.10
Organic acids	HMDB0000193	C00311	Isocitric acid	0.00	0.06	2.32	1.21	1.29
	HMDB0000641	C00064	Glutamine	0.04	0.27	1.26	0.33	1.85
	HMDB0000684	C00328	Kynurenine	0.02	0.15	1.53	0.61	0.95
	HMDB0000158	C00082	Tyrosine	0.00	0.01	1.46	0.55	2.23
	HMDB0002931	NA	N-acetylserine	0.03	0.21	1.18	0.24	0.83
Fatty acids	HMDB0003229	C08362	Palmitoleic acid	0.03	0.25	1.60	0.68	1.07
Phenylpropanoic acids	HMDB0000779	NA	Phenyllactic acid	0.03	0.25	20.79	4.38	1.84
Benzoic acids	HMDB0002107	C01606	Phthalic acid	0.01	0.14	1.33	0.41	2.21
SCFAs	HMDB0000237	C00163	Propionic acid	0.01	0.08	4.41	2.14	2.19
Bile acids	HMDB0000951	C05465	TCDCA	0.00	0.00	9.63	3.27	1.75
	HMDB0000036	C05122	TCA	0.01	0.09	9.75	3.28	1.54

GCDCA: Glycochenodeoxycholic acid; TCA: Tricarboxylic acid; TCDCA: Taurochenodeoxycholic acid; NA: Not Applicable; DHA: Docosahexaenoic acid; DPA: Docosapentaenoic acid; EPA: Eicosapentaenoic acid; UDCA: Ursodeoxycholic acid; CA: Citric acid; GABA: Gamma-amino butyric acid.

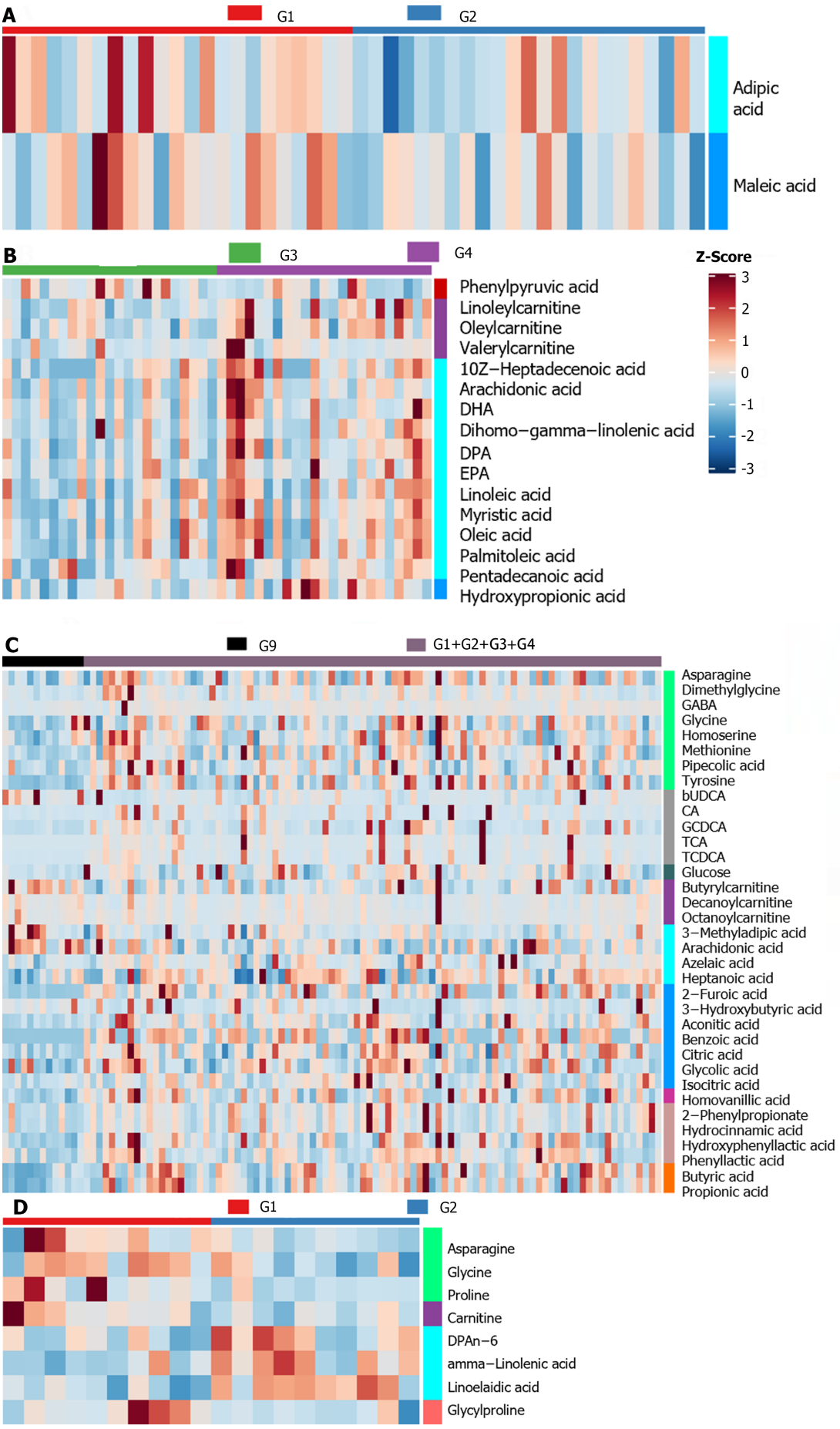


DOI: 10.4254/wjh.v15.i9.1043

Figure 2 Volcano plot of serum metabolites. A: Volcano plot of entecavir responders (E-R) *vs* entecavir no-responders (E-N) (training set); B: Volcano plot of FuzhengHuayu tablet (FZHY) + entecavir responders (F-R) *vs* FZHY + entecavir no-responders (F-N) (training set); C: Volcano plot of patients *vs* volunteers (training set); D: Volcano plot of E-R *vs* E-N (validation set); E: Volcano plot of F-R *vs* F-N (validation set); F: Volcano plot of patients *vs* volunteers (validation set).

Metabolic pathways related to the selected metabolites in different sets

Both topological centrality (impact value > 0) and enrichment significance [-ln(p) > 2.99, namely $P < 0.05$] were used to evaluate the analyses of enrichment and metabolic pathways for the selected potential metabolites. As shown in Figure 4, there were 2 pathways (butanoate metabolism, nicotinate and nicotinamide metabolism) (E-R *vs* E-N), 1 pathway (fatty acid biosynthesis) (F-R *vs* F-N), and 11 pathways (primary bile acid biosynthesis, nitrogen metabolism, butanoate metabolism, aminoacyl-tRNA biosynthesis, cyanoamino acid metabolism, phenylalanine metabolism, glycine, serine and threonine metabolism, glyoxylate and dicarboxylate metabolism, citrate cycle (TCA cycle), thiamine metabolism, alanine, aspartate and glutamate metabolism) (patients *vs* volunteers) in the training set (Figure 4A-C); and there were 6 pathways (aminoacyl-tRNA biosynthesis, cyanoamino acid metabolism, nitrogen metabolism, linoleic acid metabolism, thiamine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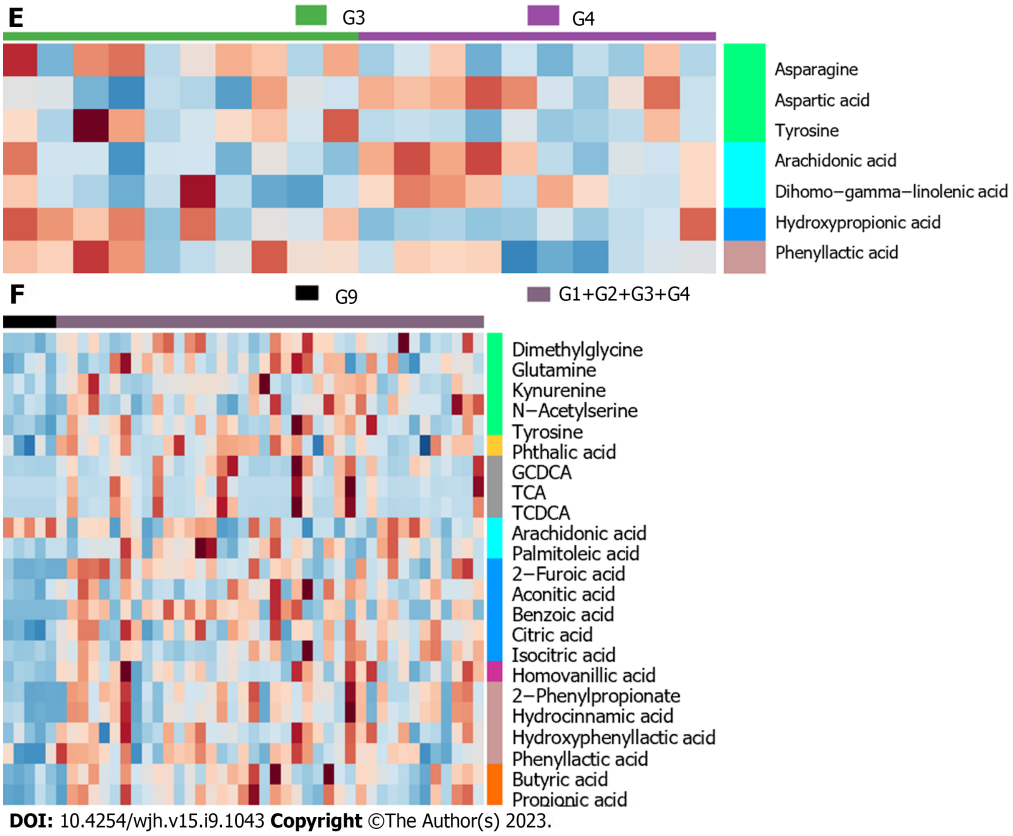
G1
G2
Adipic acid
Maleic acid
B
G3
G4
Z-Score
3
2
1
0
-1
-2
-3
Phenylpyruvic acid
Linoleylcarnitine
Oleylcarnitine
Valerylcarnitine
10Z−Heptadecenoic acid
Arachidonic acid
DHA
Dihomo−gamma−linolenic acid
DPA
EPA
Linoleic acid
Myristic acid
Oleic acid
Palmitoleic acid
Pentadecanoic acid
Hydroxypropionic acid
C
G9
G1+G2+G3+G4
Asparagine
Dimethylglycine
GABA
Glycine
Homoserine
Methionine
Pipecolic acid
Tyrosine
bUDCA
CA
GCDCA
TCA
TCDCA
Glucose
Butyrylcarnitine
Decanoylcarnitine
Octanoylcarnitine
3−Methyladipic acid
Arachidonic acid
Azelaic acid
Heptanoic acid
2−Furoic acid
3−Hydroxybutyric acid
Aconitic acid
Benzoic acid
Citric acid
Glycolic acid
Isocitric acid
Homovanillic acid
2−Phenylpropionate
Hydrocinnamic acid
Hydroxyphenyllactic acid
Phenyllactic acid
Butyric acid
Propionic acid
D
G1
G2
Asparagine
Glycine
Proline
Carnitine
DPAn−6
amma−Linolenic acid
Linoelaidic acid
Glycylproline



DOI: 10.4254/wjh.v15.i9.1043

Figure 3 Heatmap of all the selected potential metabolites. A: Heatmap of entecavir responders (E-R) *vs* entecavir no-responders (E-N) (training set); B: Heatmap of FuzhengHuayu tablet (FZHY) + entecavir responders (F-R) *vs* FZHY + entecavir no-responders (F-N) (training set); C: Heatmap of patients *vs* volunteers (training set); D: Heatmap of E-R *vs* E-N (validation set); E: Heatmap of F-R *vs* F-N (validation set); F: Heatmap of patients *vs* volunteers (validation set). CA: Citric acid; GCDCA: Glycochenodeoxycholic acid; TCA: Tricarboxylic acid; TCDCA: Aurochenodeoxycholic acid; DHA: Docosahexaenoic acid; DPA: Docosapentaenoic acid; EPA: Eicosapentaenoic acid.

metabolism, alanine, aspartate and glutamate metabolism) (E-R *vs* E-N), 5 pathways (nitrogen metabolism, aminoacyl-tRNA biosynthesis, cyanoamino acid metabolism, alanine, aspartate and glutamate metabolism, beta-alanine metabolism) (F-R *vs* F-N), and 6 pathways (phenylalanine metabolism, primary bile acid biosynthesis, TCA cycle, tyrosine metabolism, ubiquinone and other terpenoid-quinone biosynthesis, nitrogen metabolism) (patients *vs* volunteers) in the validation set (Figure 4D-F).

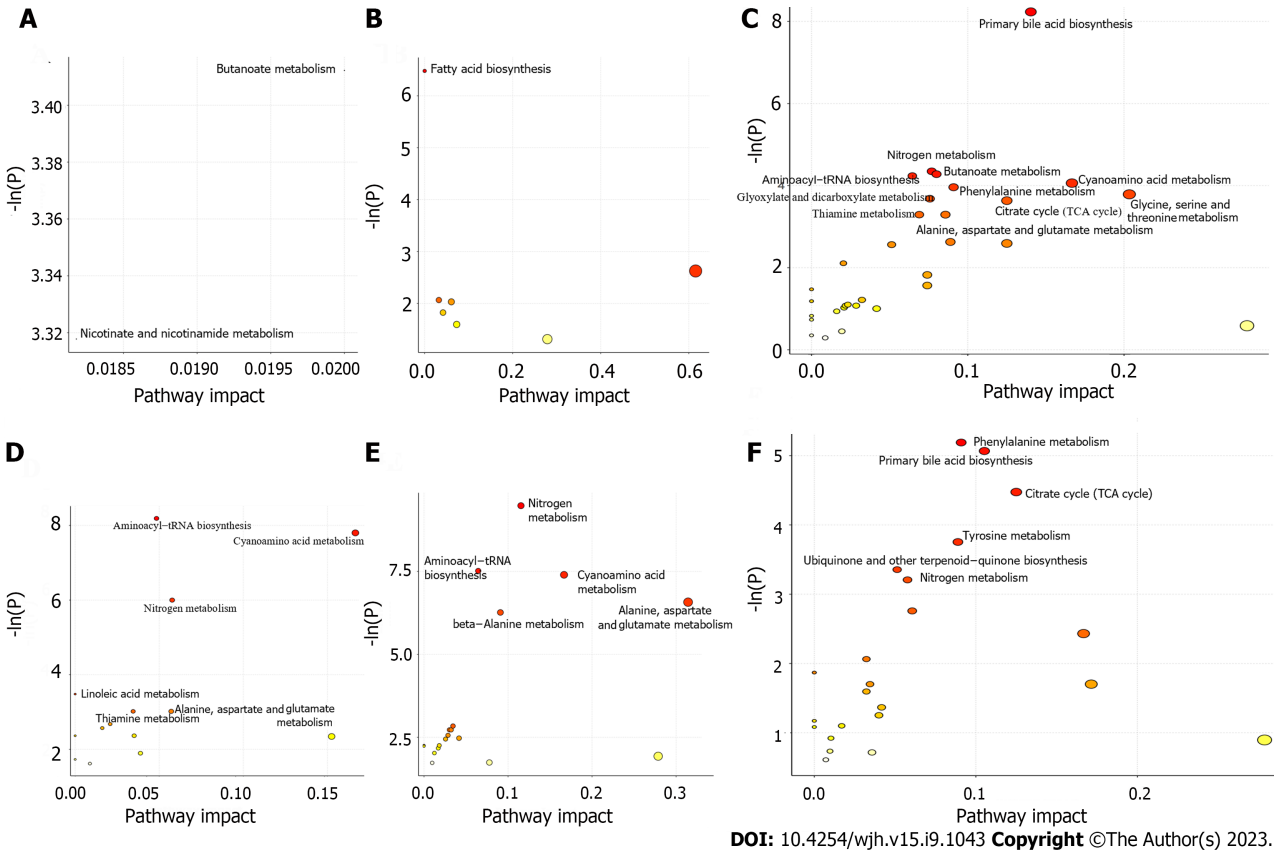
Selection of differential metabolites in different sets

In order to find differential metabolites from these selected potential metabolites, RF, SVM and Boruta analyses were conducted for each selected metabolite in sequence. And intersection of these potential metabolites in the three analyses can be found in Supplementary Figure 5. Specifically, there were Maleic acid and Adipic acid (E-R *vs* E-N), Hydroxypropionic acid, 10Z-heptadecenoic acid, and linoleylcarnitine (F-R *vs* F-N), tyrosine, benzoic acid, 2-Furoic acid, aconitic acid, and butyrylcarnitine (patients *vs* volunteers) in the training set while there were linoelaidic acid, gamma-linolenic acid, glycylproline, proline, asparagine, and carnitine (E-R *vs* E-N), hydroxypropionic acid, aspartic acid, dihomo-gamma-linolenic acid, and tyrosine (F-R *vs* F-N), dimethylglycine, citric acid, GCDCA, and 2-phenylpropionate (patients *vs* volunteers) in the validation set.

In the results of Boruta analysis (Figure 5), the metabolites marked as confirmed are the differential metabolites obtained by the final screening for subsequent model construction. As shown in Figure 5A-C, in addition to the above intersection metabolites, there were arachidonic acid, oleylcarnitine, and docosahexaenoic acid (F-R *vs* F-N), butyric acid, TCDCA, arachidonic acid, citric acid, and propionic acid (patients *vs* volunteers) confirmed in the training set. As shown in Figure 5D-F, in addition to the above intersection metabolites, there were TCDCA, benzoic acid, tyrosine, 2-Furoic acid, butyric acid, TCA, isocitric acid, hydrocinnamic acid, and propionic acid (patients *vs* volunteers) confirmed in the validation set.

Evaluation of model effects in different sets

In the training set, there were good sensitivity and specificity with the AUC value of 0.851 (F-R *vs* F-N) and 0.985 (patients *vs* volunteers) except for 0.733 (E-R *vs* E-N) (Figure 6A-C). In the validation set, there were good sensitivity and specificity with the AUC value of 1 (E-R *vs* E-N, patients *vs* volunteers) and 0.94 (F-R *vs* F-N) (Figure 6D-F). On the whole, the above AUC values of the two sets indicated good diagnostic capability in this study.



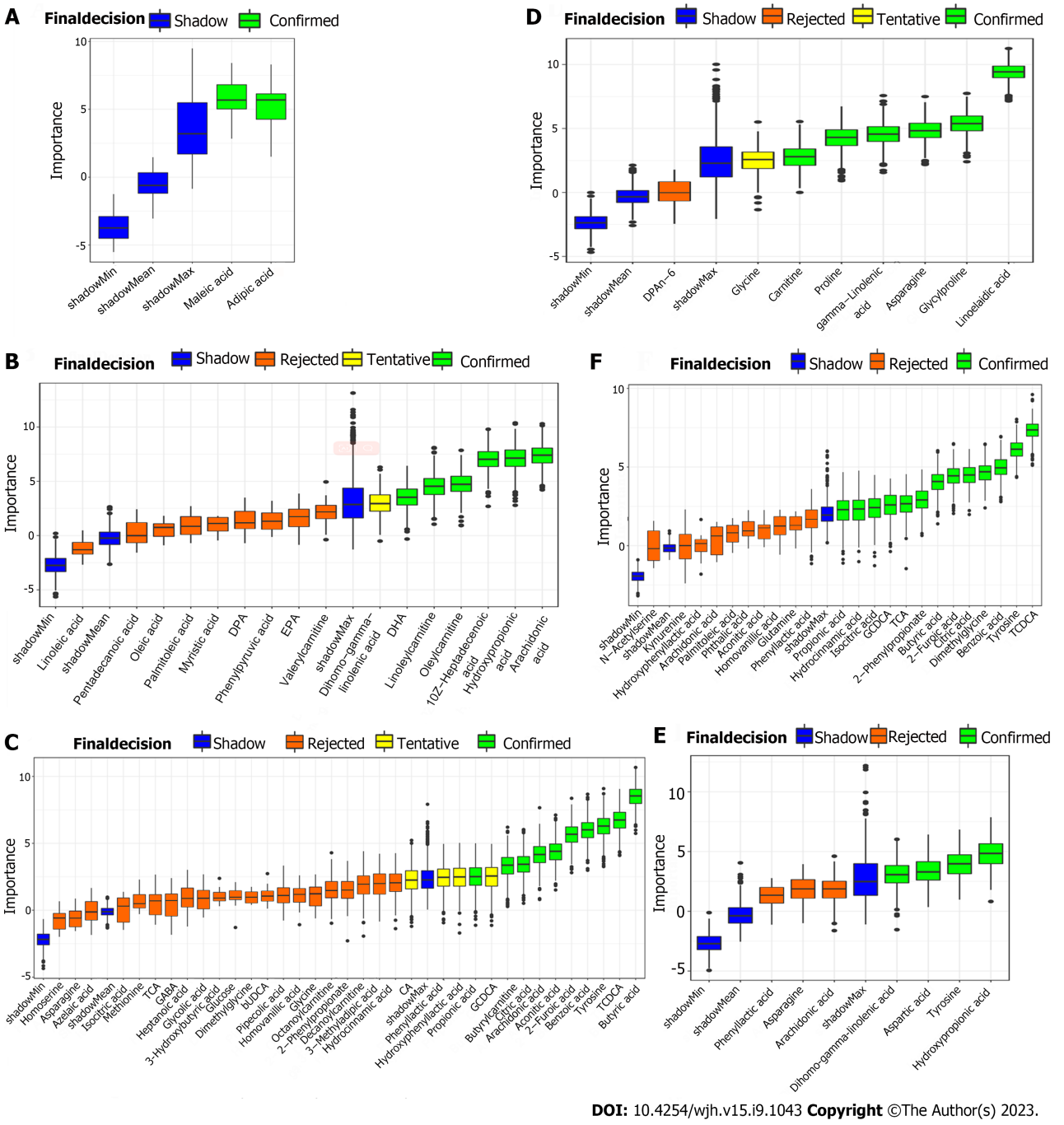
DOI: 10.4254/wjh.v15.i9.1043

Figure 4 Bubbleplot of the selected metabolites pathways. A: Bubbleplot of entecavir responders (E-R) *vs* entecavir no-responders (E-N) (training set); B: Bubbleplot of FuzhengHuayu tablet (FZHY) + entecavir responders (F-R) *vs* FZHY + entecavir no-responders (F-N) (training set); C: Bubbleplot of patients *vs* volunteers (training set); D: Bubbleplot of E-R *vs* E-N (validation set); E: Bubbleplot of F-R *vs* F-N (validation set); F: Bubbleplot of patients *vs* volunteers (validation set). TCA: Tricarboxylic acid.

DISCUSSION

With the global prevalence of HBV-related liver fibrosis on the rise, precise targeting of the population that responds to entecavir or entecavir + FZHY is of paramount importance for improving clinical efficacy through precision treatment. Metabolomics serves as a valuable tool for biomarker discovery[18]. In this study, we employed HPLC-MS and advanced multivariate statistical modeling to predict the serum differential metabolites associated with interventions effectively reversing HBV-related liver fibrosis. Our findings revealed the involvement of 7 metabolic pathways (E-R *vs* E-N), including linoleic acid metabolism, aminoacyl-tRNA biosynthesis, cyanoamino acid metabolism, alanine, aspartate, and glutamate metabolism, nitrogen metabolism, butanoate metabolism, and nicotinate and nicotinamide metabolism. Similarly, 7 metabolic pathways (F-R *vs* F-N) were identified, encompassing linoleic acid metabolism, aminoacyl-tRNA biosynthesis, cyanoamino acid metabolism, alanine, aspartate, and glutamate metabolism, nitrogen metabolism, beta-alanine metabolism, and fatty acid biosynthesis. Furthermore, 3 metabolic pathways (patients *vs*. volunteers) were noted, which included nitrogen metabolism, primary bile acid biosynthesis, and the TCA cycle. Regarding the intersection of differential metabolic pathways between the E-R *vs* E-N and F-R *vs* F-N groups, our study highlighted 4 common pathways: Linoleic acid metabolism, aminoacyl-tRNA biosynthesis, cyanoamino acid metabolism, and alanine, aspartate, and glutamate metabolism.

Regarding linoleic acid metabolism, a study suggested an inverse association between dietary linoleic acid intake and the risk of significant liver fibrosis, particularly emphasizing the ratio of unsaturated to saturated fatty acids[19]. Another clinical investigation demonstrated that specific alterations in linoleic acid metabolites could differentiate individuals with moderate alcohol-associated hepatitis from those with mild alcohol-associated liver disease among heavy drinkers. It is noteworthy that alcohol-associated liver diseases share common characteristics, spanning from steatosis to steatohepatitis, fibrosis, and cirrhosis[20]. Concerning aminoacyl-tRNA biosynthesis, an animal experiment revealed that Ganfule capsules could mitigate liver injury and liver fibrosis induced by bile duct ligation in mice. These effects were associated with the regulation and control of metabolic pathways, including glutamine metabolism, valine, leucine, and isoleucine biosynthesis, as well as aminoacyl-tRNA biosynthesis[21]. Furthermore, findings from a nonalcoholic fatty liver disease rat model indicated that metabolic disturbances primarily revolved around aminoacyl-tRNA biosynthesis, nitrogen metabolism, lipid metabolism, glyoxylate and dicarboxylate metabolism, and amino metabolism[22]. As for alanine, aspartate, and glutamate metabolism, a study aimed at investigating the role of the Wnt/β-catenin signaling pathway and the enzyme l-glutaminase in liver fibrosis pathogenesis and the potential benefits of niclosamide in treating liver fibrosis. It was observed that the group of rats treated with niclosamide and CC cytokine ligand-4 exhibited significant reductions

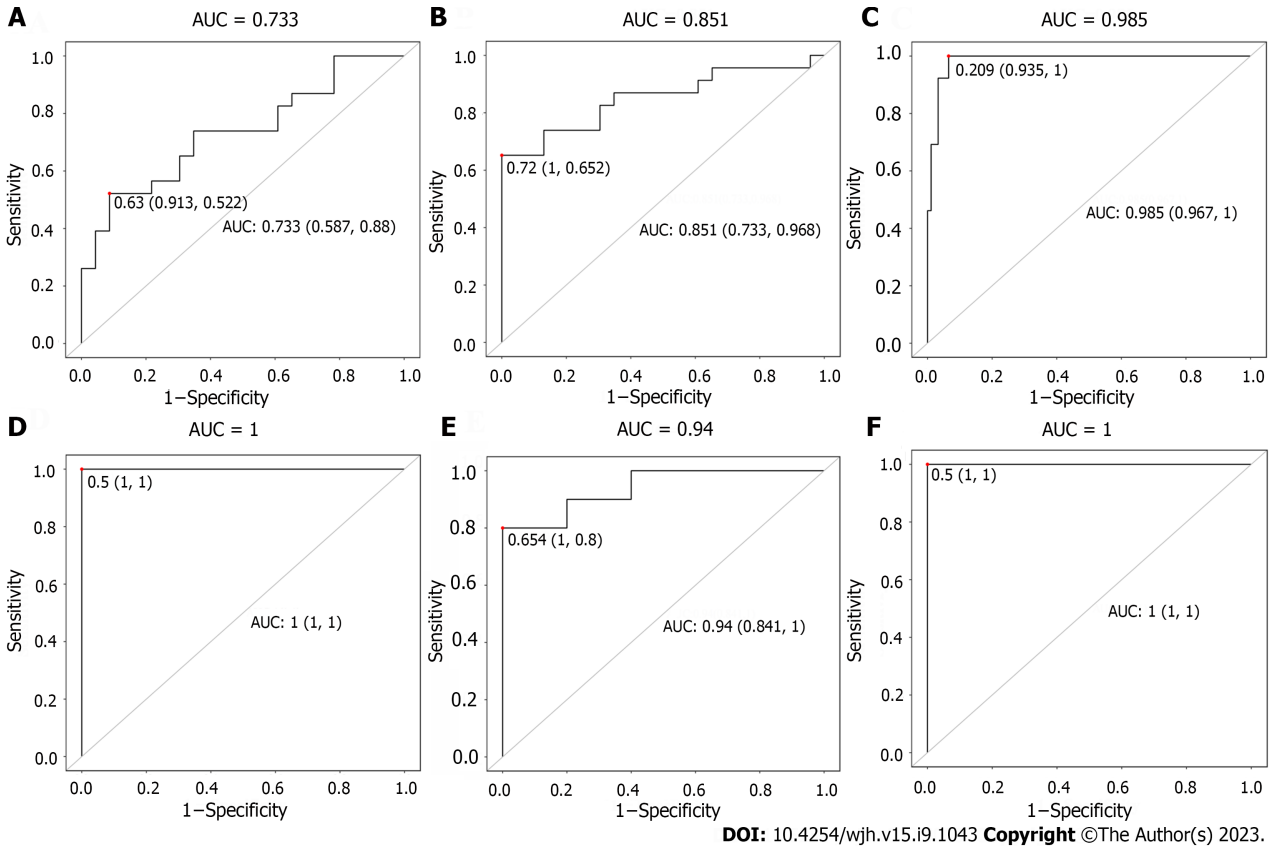


DOI: 10.4254/wjh.v15.i9.1043

Figure 5 Boxplot of all the differential metabolites. A: Boxplot of entecavir responders (E-R) *vs* entecavir no-responders (E-N) (training set); B: Boxplot of FuzhengHuayu tablet (FZHY) + entecavir responders (F-R) *vs* FZHY + entecavir no-responders (F-N) (training set); C: Boxplot of patients *vs* volunteers (training set); D: Boxplot of E-R *vs* E-N (validation set); E: Boxplot of F-R *vs* F-N (validation set); F: Boxplot of patients *vs* volunteers (validation set).

in TBIL, alanine transaminase, aspartate transaminase, β-catenin, l-hydroxyproline, and l-glutaminase activity. These findings led to the conclusion that Niclosamide protected rats against liver fibrosis by inhibiting the Wnt/β-catenin pathway and glutaminolysis[23]. In summary, the metabolic pathways identified in this study are intricately linked to the initiation and progression of liver fibrosis.

The investigation into baseline differential metabolites for predicting the response to entecavir or entecavir + FZHY in HBV-related fibrotic livers has unveiled crucial insights with the potential to enhance tailored treatments for individuals. Notably, our findings indicated that specific differential metabolites, as mentioned earlier, were closely associated with the response to entecavir and entecavir + FZHY in HBV-related fibrotic livers. Furthermore, this study proposed that these baseline differential metabolites could be effectively combined with clinical parameters to enhance the precision of personalized treatment for patients grappling with HBV-related liver fibrosis. This approach holds the key to reducing the incidence of treatment failures stemming from inappropriate therapeutic interventions. Moreover, the insights gleaned from this research bear significant implications for the advancement of biomarker-guided precision medicine. These differential metabolites can potentially be employed to predict disease progression, select the most suitable treatment modalities, and monitor treatment outcomes among HBV patients. Additionally, this study provides a



DOI: 10.4254/wjh.v15.i9.1043

Figure 6 Receiver operating characteristic curve of all the differential metabolites. A: Receiver operating characteristic (ROC) curve of entecavir responders (E-R) *vs* entecavir no-responders (E-N) (training set); B: ROC curve of FuzhengHuayu tablet (FZHY) + entecavir responders (F-R) *vs* FZHY + entecavir no-responders (F-N) (training set); C: ROC curve of patients *vs* volunteers (training set); D: ROC curve of E-R *vs* E-N (validation set); E: ROC curve of F-R *vs* F-N (validation set); F: ROC curve of patients *vs* volunteers (validation set). AUC: Area under the curve.

foundation for the exploration of novel metabolites or biomarkers that might serve as superior predictors of the response to entecavir or entecavir + FZHY in HBV-related fibrotic livers. Ultimately, these findings contribute to an enhanced understanding of the molecular mechanisms underpinning HBV-related liver fibrosis and may offer opportunities to more accurately evaluate the efficacy of individualized treatments. By comprehending the intricate association between these differential metabolites and the response to entecavir and entecavir + FZHY, healthcare practitioners can fine-tune treatment options for each patient, thereby optimizing the effectiveness of HBV-related liver fibrosis therapy. Furthermore, the outcomes of this study can serve as a valuable resource for the development of future pharmacological treatments that target different pathways more effectively in combatting HBV-related liver fibrosis.

There are several noteworthy limitations in our study. Firstly, all of our sample sources were confined to China. This geographically limited distribution could potentially restrict the broader applicability of our therapeutic regimen. Secondly, there was no dedicated FZHY monotherapy group. Given that all participants included in our study were CHB patients, and the development of liver fibrosis in these individuals was directly or indirectly attributed to HBV infection, antiviral therapy was considered the foundational treatment. Administering FZHY as the sole treatment to HBV-related liver fibrosis patients would be ethically inconsistent with clinical standards. Consequently, we lacked an observation of the therapeutic efficacy of FZHY in isolation. In regard to the FZHY monotherapy group, for future research endeavors, it may be considered to further validate the identified differential metabolites and metabolic pathways by selecting alternative etiologies of liver fibrosis for validation or by investigating the distinctions between monotherapy and combination therapy in animal experiments. Thirdly, our study exclusively focused on patients with hepatitis B, and whether our conclusions can be extrapolated to the treatment of liver fibrosis arising from other causes necessitates further exploration. Lastly, due to the cross-sectional nature of our study, external reproducibility should be further evaluated through prospective studies.

CONCLUSION

In summary, through metabolomis analysis, we have identified 4 metabolic pathways and 7 differential metabolites from serum that accurately differentiated responders from no-responders in the treatment of HBV-related liver fibrosis. If validated in future studies, these metabolic pathways and differential metabolites will be useful in improving the curative effect of entecavir + FZHY and promoting the development of precision medicine.

ARTICLE HIGHLIGHTS

Research background

After receiving entecavir or combined with FuzhengHuayu tablet (FZHY) treatment, some sufferers with hepatitis B virus (HBV)-related liver fibrosis could achieve a histological improvement while the others may fail to improve even worsen. Serum metabolomics at baseline in these patients who were effective in treatment remain unclear.

Research motivation

The key significance of this cross-sectional study is to predict the serum metabolites of the treatment (entecavir or entecavir + FZHY) that effectively reversed HBV-related liver fibrosis.

Research objectives

We are about to explore serum differential metabolites and metabolic pathways at baseline in HBV-related liver fibrosis patients who are response to the treatments.

Research methods

A total of 132 patients with HBV-related liver fibrosis and 18 volunteers as healthy controls were recruited. First, all subjects were divided into training set and validation set. Second, the included patients were subdivided into entecavir responders (E-R), entecavir no-responders (E-N), FZHY + entecavir responders (F-R), and FZHY + entecavir no-responders (F-N) following the pathological histological changes after 48 wk' treatments. Then, serum samples of all subjects before treatment were tested by high-performance liquid chromatography-tandem mass spectrometry. Data processing was conducted using multivariate principal component analysis and orthogonal partial least squares discriminant analysis. Diagnostic tests of selected differential metabolites were used for Boruta analyses and logistic regression.

Research results

As for the intersection about differential metabolic pathways between the groups E-R *vs* E-N and F-R *vs* F-N, results showed that 4 pathways including Linoleic acid metabolism, aminoacyl-tRNA biosynthesis, cyanoamino acid metabolism, alanine, aspartate and glutamate metabolism were screened out. As for the differential metabolites, these 7 intersected metabolites including hydroxypropionic acid, tyrosine, citric acid, taurochenodeoxycholic acid, benzoic acid, 2-furoic acid, and propionic acid were selected.

Research conclusions

Our findings showed that 4 metabolic pathways and 7 differential metabolites have potential usefulness in clinical prediction of the response of entecavir or combined with FZHY on HBV fibrotic liver.

Research perspectives

It is of great theoretical and practical significance to prevent the transformation of liver fibrosis to cirrhosis or even hepatocellular carcinoma and reduce the social burden.

FOOTNOTES

Author contributions: Liu CH and Zhao ZM conceived and designed the study; Dai YK, Fan HN, Huang K and Sun X performed the experiment; Dai YK, Fan HN, Huang K and Sun X analyzed the data; Dai YK wrote the paper; Liu CH and Zhao ZM contributed to supervision; All authors approved the final manuscript as submitted.

Supported by National Science and Technology Major Project, No. 2014ZX10005001 and No. 2018ZX10302204; National Natural Science Foundation of China, No. 81730109 and No. 82274305; Shanghai Key Specialty of Traditional Chinese Clinical Medicine, No. shslczdzk01201; China Postdoctoral Science Foundation, No. 2022M722162; Siming Youth Fund of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, No. SGKJ-202104.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Yun-Kai Dai 0000-0002-1667-4670; Hai-Na Fan 0000-0002-5565-4875; Kai Huang 0000-0002-7294-8015; Xin Sun 0000 0001 5480 8062; Zhi-Min Zhao 0000-0002-0424-6089; Cheng-Hai Liu 0000-0002-1696-6008.

S-Editor: Qu XL
L-Editor: A
P-Editor: Cai YX

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World J Hepatol 2023 September 27; 15(9): 1060-1083

DOI: 10.4254/wjh.v15.i9.1060

ISSN 1948-5182 (online)

META-ANALYSIS

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

Vasileios Periklis Papadopoulos, Konstantinos Mimidis

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Moreno-Gómez-Toledano R, Spain; Sholkamy A, Egypt

Received: July 16, 2023
Peer-review started: July 16, 2023
First decision: August 4, 2023
Revised: August 13, 2023
Accepted: August 29, 2023
Article in press: August 29, 2023
Published online: September 27, 2023

Vasileios Periklis Papadopoulos, Dialysis, AKESIOS Dialysis Center, Xanthi 67150, Greece

Konstantinos Mimidis, First Department of Internal Medicine, Democritus University of Thrace, Alexandroupolis 68100, Greece

Corresponding author: Vasileios Periklis Papadopoulos, MD, MSc, PhD, Consultant Physician-Scientist, Research Fellow, Dialysis, AKESIOS Dialysis Center, Vaniano, Xanthi 67150, Greece. vaspapmd@gmail.com

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.

Citation: Papadopoulos VP, Mimidis K. Corrected QT interval in cirrhosis: A systematic review and meta-analysis. *World J Hepatol* 2023; 15(9): 1060-1083

URL: https://www.wjgnet.com/1948-5182/full/v15/i9/1060.htm

DOI: https://dx.doi.org/10.4254/wjh.v15.i9.1060

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

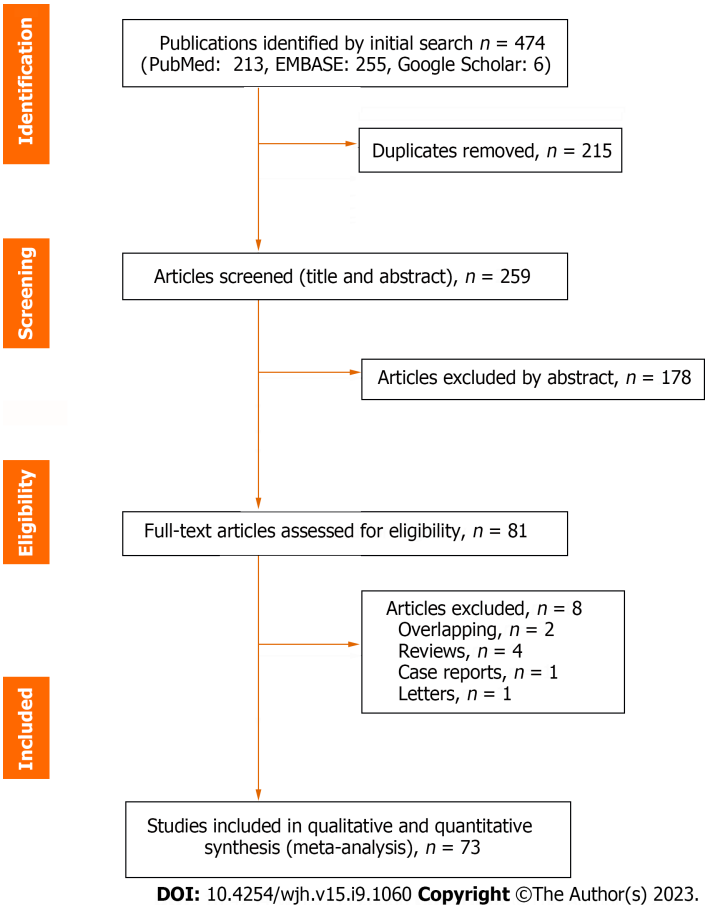
Data concerning first author, year of publication, type of study, method used, sample size, mean age, female ratio, alcoholic etiology of cirrhosis ratio, Child-Pugh A/B/C ratio, mean MELD score, use of β-blockers, formula for QT correction, mean pulse rate, QTc in patients with cirrhosis and controls, 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



DOI: 10.4254/wjh.v15.i9.1060

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

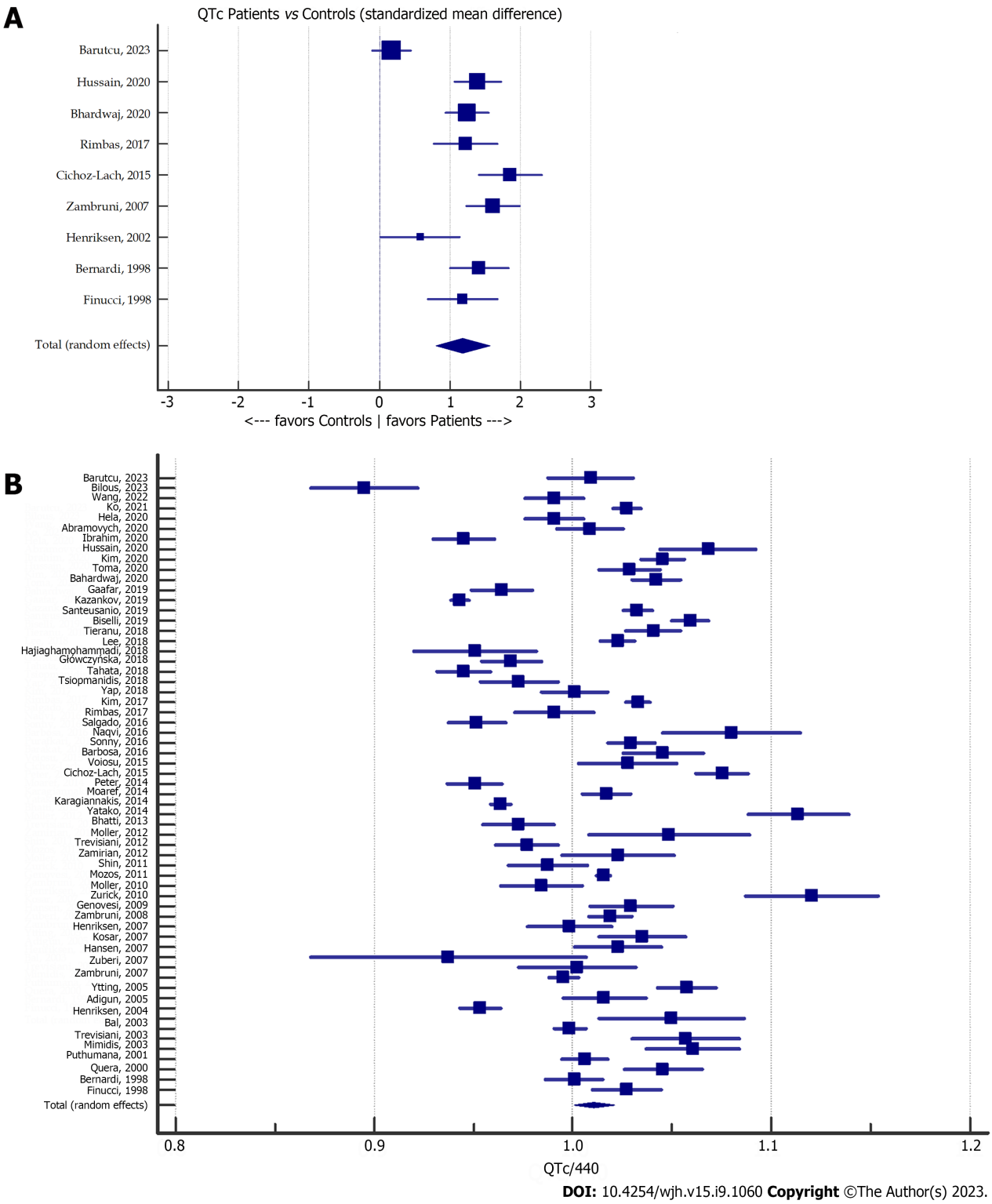
QTc was comparable between male and female patients (SMD = -0.032; 95%CI: -0.229 to 0.165; $P = 0.753$); I^2 was 78.5% (95%CI: 62.0%-87.8%; $P < 0.001$) (Figure 4A). Moreover, no correlation of QTc with age ($P = 0.974$) was detected, even after adjustment for alcoholic etiology rate and MELD score ($P_{adj}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

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-



DOI: 10.4254/wjh.v15.i9.1060

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).

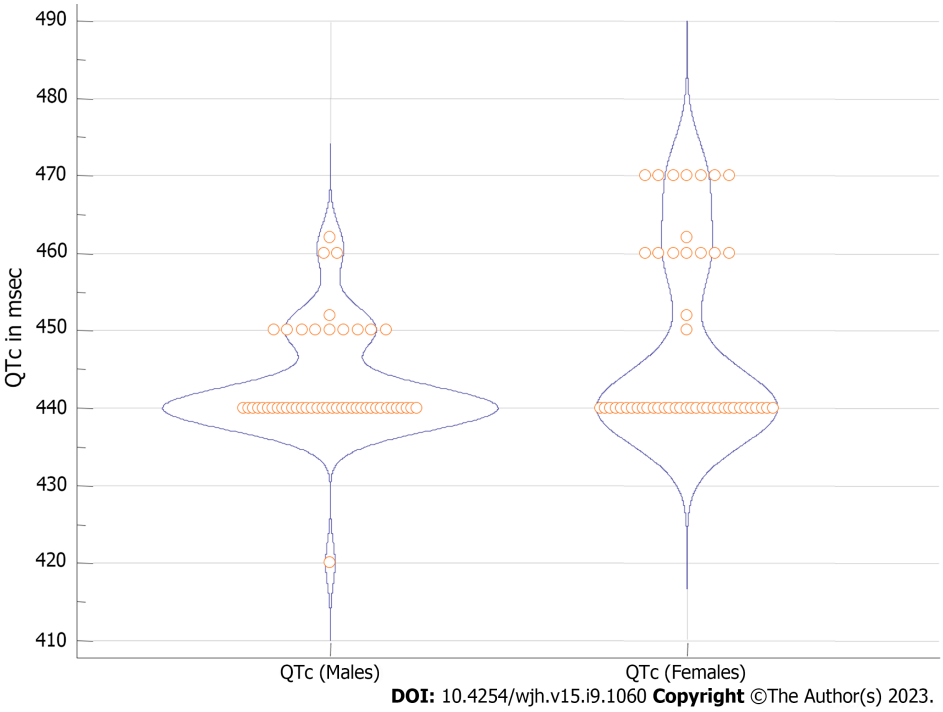


Figure 3 Violi plot for corrected QT upper normal limit used in the included studies. QTc: Corrected QT.

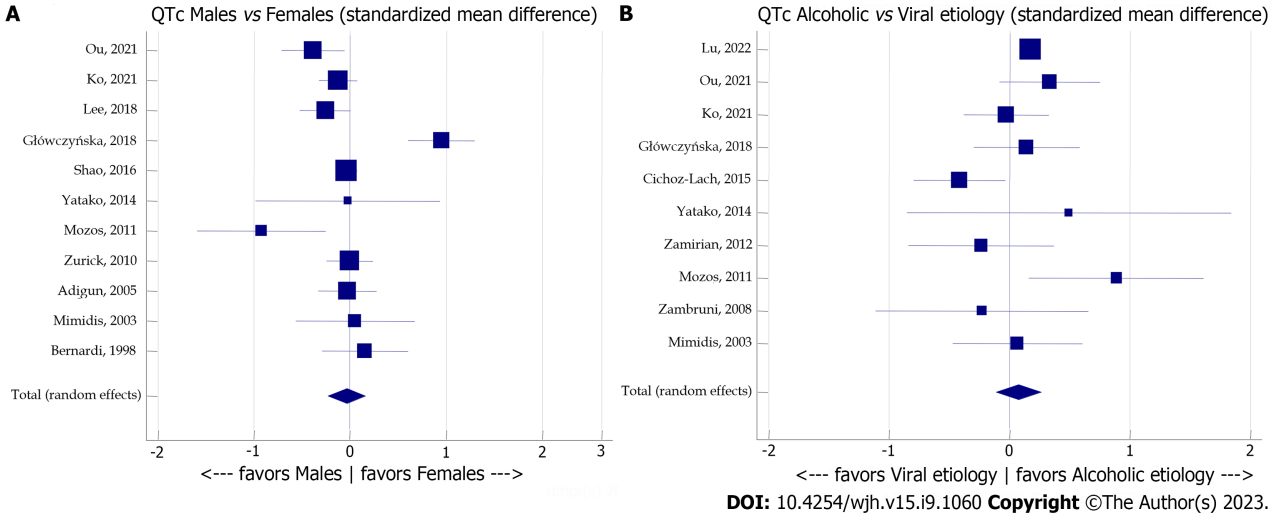


Figure 4 Meta-analysis forest plot concerning the effect of sex and etiology of cirrhosis on corrected QT. A: The effect of sex on corrected QT (QTc) in patients with cirrhosis; B: The effect of etiology of cirrhosis on QTc. QTc: Corrected QT.

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).

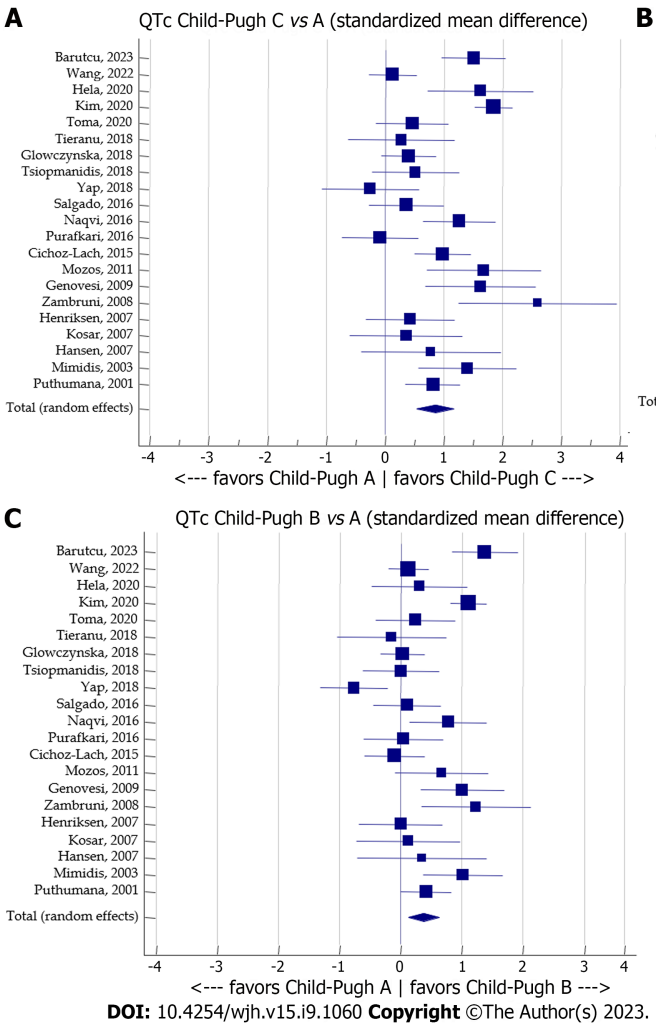


Figure 5 Meta-analysis forest plots concerning the effect of the Child-Pugh stage on corrected QT. A: Child-Pugh stage C *vs* A; B: Child-Pugh stage C *vs* B; C: Child-Pugh stage B *vs* A. QTc: Corrected QT.

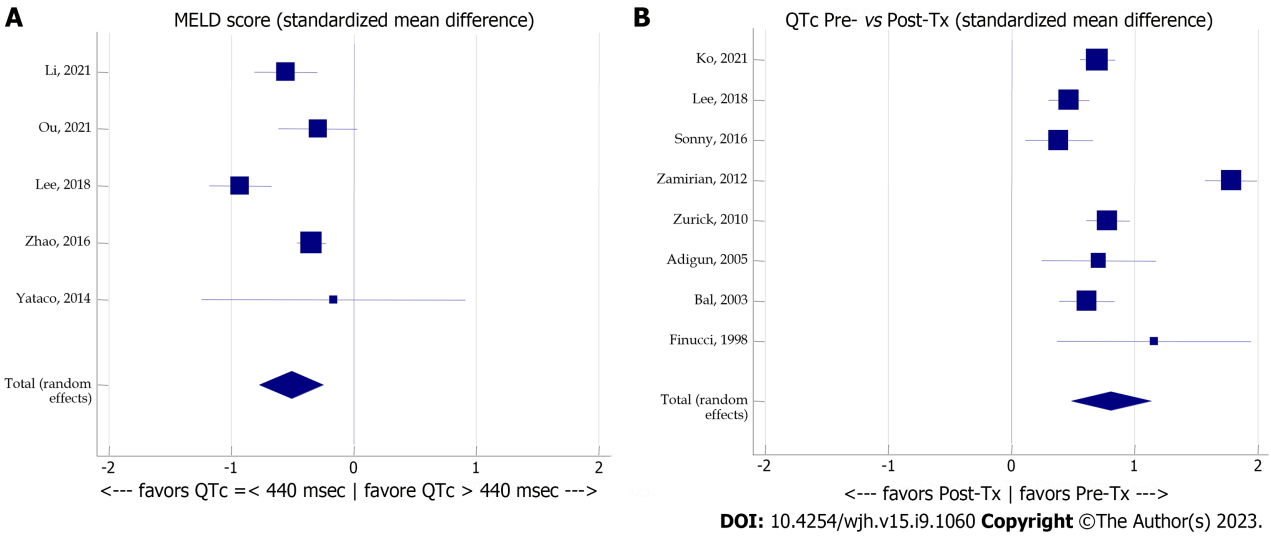


Figure 6 Meta-analysis forest plot concerning the effect of the model for end-stage liver disease score and liver transplantation on corrected QT. A: The effect of the model for end-stage liver disease score on corrected QT (QTc); B: The effect of liver transplantation on QTc. Tx: Transplantation; MELD: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

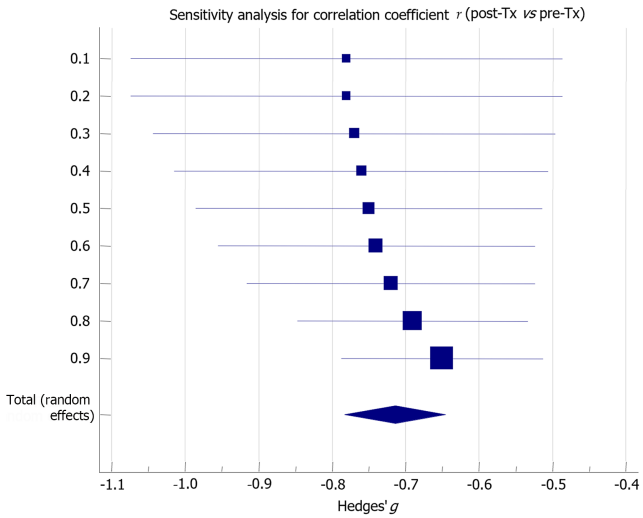
Endpoint	Risk of bias	Imprecision	Inconsistency	Indirectness	Publication bias	Effect size	Quality
Cirrhosis effect (patients *vs* controls) on QTc	No important risk of bias	No important imprecision	No important inconsistency	No important indirectness	No important publication bias	Very large	Very high
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.

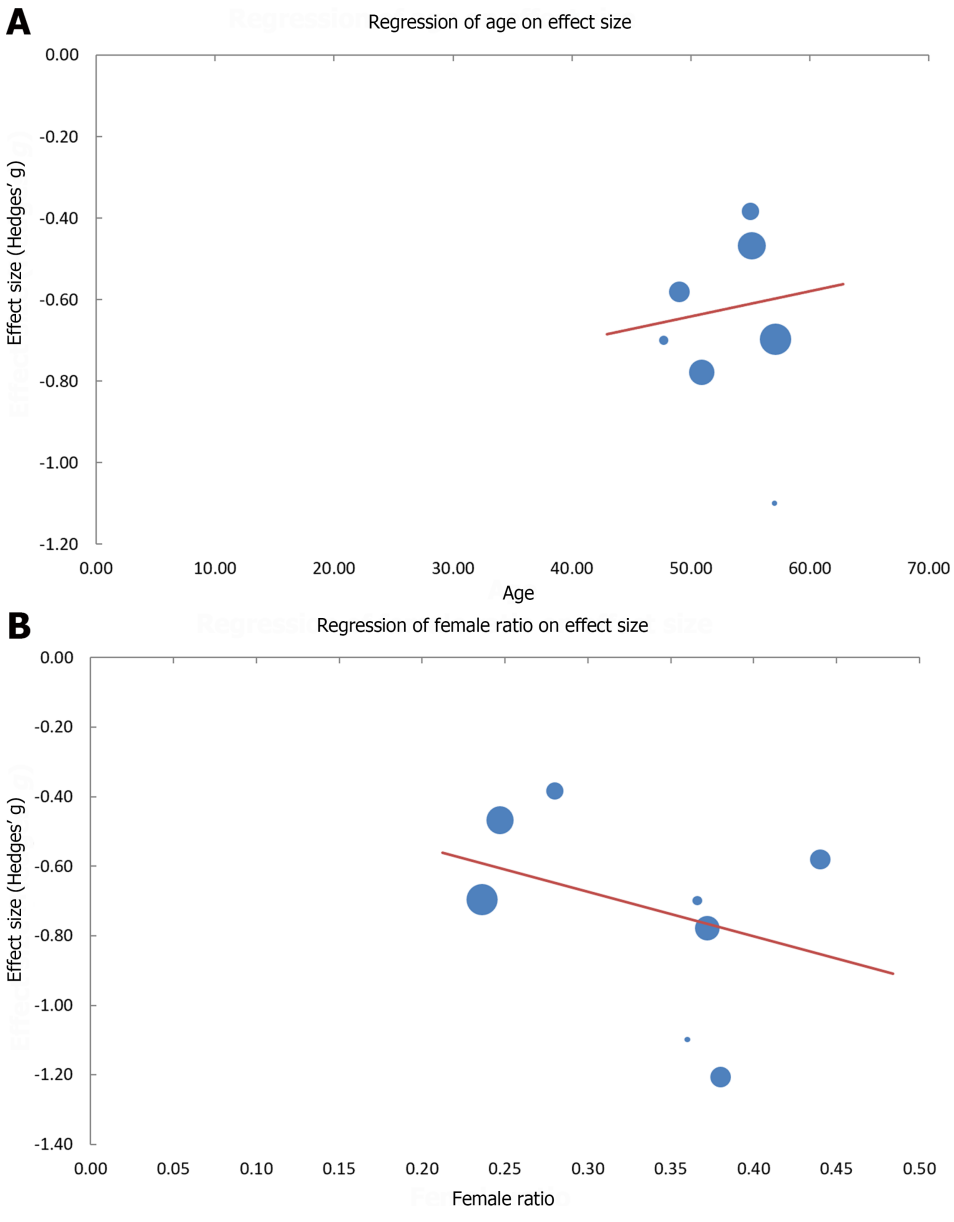
It is widely debated which upper normal limit should be used for QTc in patients with cirrhosis. In contrast with what is considered as QTc upper normal limit for patients without cirrhosis, namely < 430 ms for males and < 450 ms for females, 440 ms was adopted as the upper normal limit for QTc for both 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



DOI: 10.4254/wjh.v15.i9.1060

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



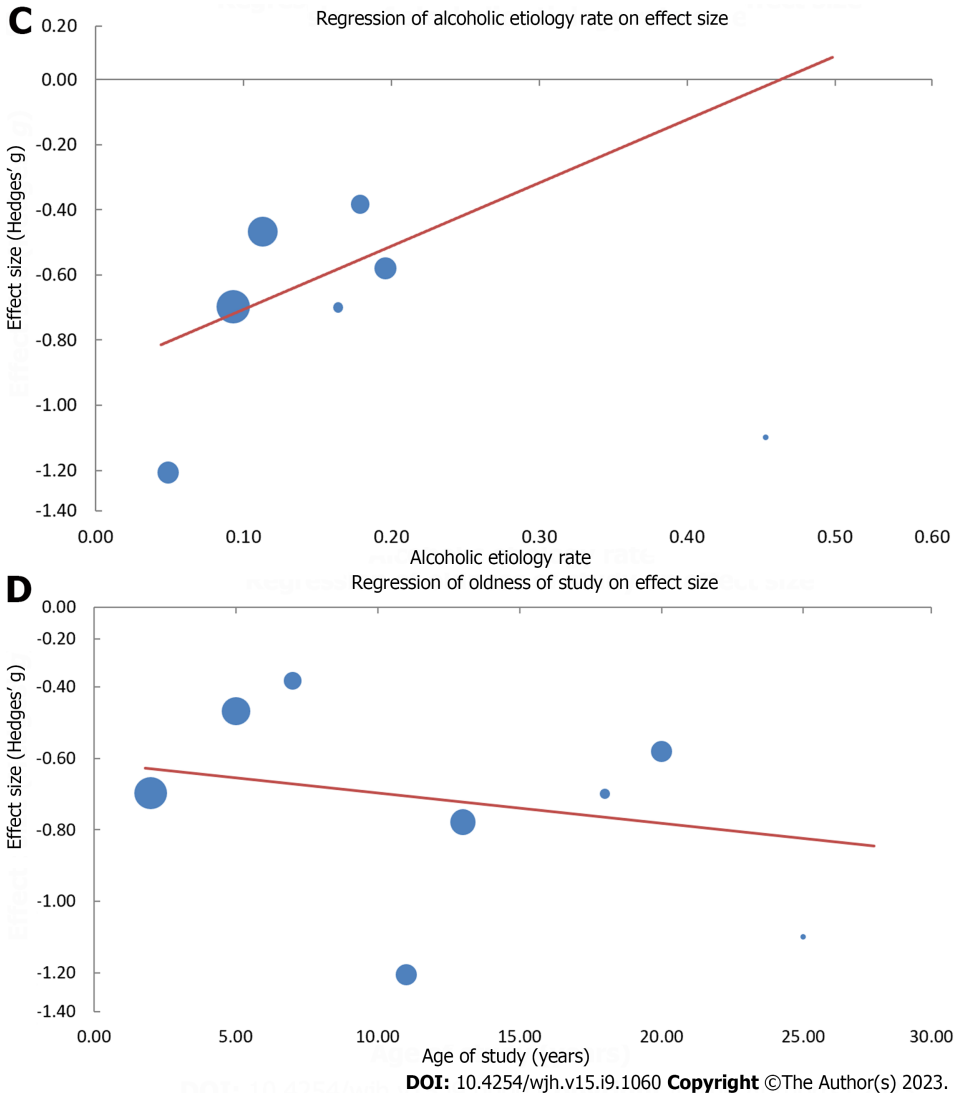


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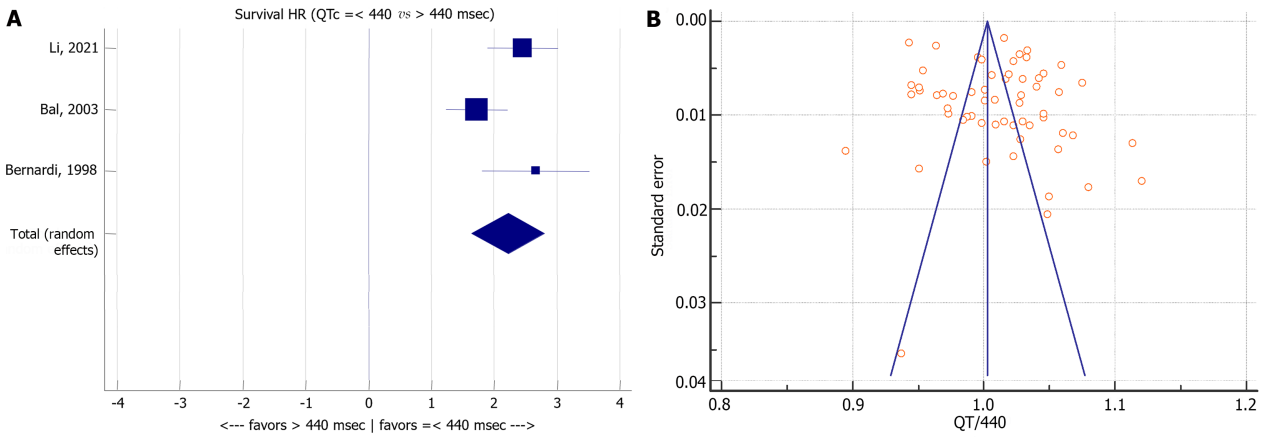
Figure 8 Plot points and regression lines on effect size, namely Hedges' *g*, reflecting correlations of pre-transplantation *vs* post-transplantation corrected QT. A: Age [H_g = -0.95 + 0.01 (yr); *P* = 0.417]; B: Female ratio [H_g = -0.29 - 1.28 (female ratio); *P* < 0.001]; C: Alcoholic etiology rate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

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: Greece

ORCID number: Vasileios Periklis Papadopoulos 0000-0002-4188-9518; Konstantinos Mimidis 0000-0002-0783-226X.

S-Editor: Wang JJ
L-Editor: Filipodia
P-Editor: Cai YX

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