World Journal of Gastrointestinal Surgery

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

World J Gastrointest Surg 2024 February 27; 16(2): 481-490

DOI: 10.4240/wjgs.v16.i2.481

ISSN 1948-9366 (online)

ORIGINAL ARTICLE

Retrospective Study

Correlation between serum markers and transjugular intrahepatic portosystemic shunt prognosis in patients with cirrhotic ascites

Xiao-Gang Hu, Xiao-Xian Yang, Jun Lu, Gang Li, Jian-Ji Dai, Jia-Min Wang, Yi Deng, Rui Feng

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): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Paula Ceballos M, Argentina

Received: November 30, 2023
Peer-review started: November 30, 2023
First decision: December 18, 2023
Revised: December 30, 2023
Accepted: January 29, 2024
Article in press: January 29, 2024
Published online: February 27, 2024

Xiao-Gang Hu, Jun Lu, Gang Li, Jian-Ji Dai, Jia-Min Wang, Yi Deng, Department of Interventional Radiology, The Affiliated Jinhua Hospital, Zhejiang University School of Medicine, Jinhua 321000, Zhejiang Province, China

Xiao-Xian Yang, Medical College, Jinhua Polytechnic, Jinhua 321017, Zhejiang Province, China

Rui Feng, Department of Interventional Medicine, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, Hangzhou 310000, Zhejiang Province, China

Corresponding author: Rui Feng, MM, Attending Doctor, Department of Interventional Medicine, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, No. 158 Shangtang Road, Hangzhou 310000, Zhejiang Province, China.
fengrui596@yeah.net

Abstract

BACKGROUND

Individuals with refractory ascites in the context of liver cirrhosis typically face an adverse prognosis. The transjugular intrahepatic portosystemic shunt (TIPS) is an efficacious intervention, but there is a lack of reliable tools for postoperative prognosis assessment. Previously utilized clinical biochemical markers, such as the serum albumin concentration (Alb), sodium (Na^+) concentration, and serum creatinine (Scr), have limited predictive value. Therefore, the quest for novel, specific biomarkers to evaluate the post-TIPS prognosis in patients with liver cirrhosis and refractory ascites holds significant practical importance.

AIM

To investigate the associations between the Child-Pugh score, model for end-stage liver disease (MELD) score, and serum cystatin C (Cys C) level and post-TIPS prognosis in patients with liver cirrhosis and refractory ascites.

METHODS

A retrospective analysis was conducted on 75 patients with liver cirrhosis and refractory ascites who underwent TIPS at our institution from August 2019 to August 2021. These patients were followed up regularly for two years, and the death toll was meticulously documented. The patients were allocated into a survival group (n = 45 patients) or a deceased group (n = 30 patients) based on their prognosis status. The clinical data of the two groups were collected, and Child-Pugh scores and MELD scores were calculated for analysis. Spearman

correlation analysis was carried out to evaluate the correlation of prognosis with Child-Pugh grade, MELD score, and Cys C level. Additionally, a multiple-factor analysis utilizing the Cox proportional hazard model was used to identify independent risk factors affecting the post-TIPS prognosis of patients with liver cirrhosis and refractory ascites. The receiver operating characteristic curve (ROC) ascertained the predictive value of the Cys C concentration, Child-Pugh grade, and MELD score for the prognosis of liver cirrhosis with refractory ascites in post-TIPS patients.

RESULTS

During a 2-year follow-up period, among 75 patients with liver cirrhosis and refractory ascites who underwent TIPS treatment, 30 patients (40.00%) passed away. The deceased cohort exhibited heightened aspartate aminotransferase, alanine aminotransferase, total bilirubin, Scr, prothrombin time, Cys C, international normalized ratio, Child-Pugh, and MELD scores compared to those of the survival cohort, while Alb and Na^+ levels were attenuated in the deceased group ($P < 0.05$). Spearman analysis revealed moderate to high positive correlations between prognosis and Child-Pugh score, MELD score, and Cys C level ($r = 0.709$, 0.749, 0.671, $P < 0.05$). Multivariate analysis using the Cox proportional hazard model demonstrated that the independent risk factors for post-TIPS prognosis in patients with liver cirrhosis and refractory ascites were Cys C (HR = 3.802; 95%CI: 1.313-11.015), Child-Pugh (HR = 3.030; 95%CI: 1.858-4.943), and MELD (HR = 1.222; 95%CI: 1.073-1.393) scores. ROC analysis confirmed that, compared to those of the classic prognostic models for Child-Pugh and MELD scores, the predictive accuracy of Cys C for post-TIPS prognosis in patients with liver cirrhosis and refractory ascites was slightly lower. This analysis yielded sensitivity and specificity values of 83.33% and 82.22%, respectively. The area under the curve value at this juncture was 0.883, with an optimal cutoff value set at 1.95 mg/L.

CONCLUSION

Monitoring the serum Cys C concentration is valuable for assessing the post-TIPS prognosis in patients with liver cirrhosis and refractory ascites. Predictive models based on serum Cys C levels, as opposed to Scr levels, are more beneficial for evaluating the condition and prognosis of patients with ascites due to cirrhosis.

Key Words: Liver cirrhosis; Refractory ascites; Transjugular intrahepatic portosystemic shunt; Cystatin C

Core Tip: Cirrhosis is a predominant contributor to global morbidity and mortality. This study sought to probe the relationship between Child-Pugh and model for end-stage liver disease (MELD) scores, as well as serum cystatin C (Cys C) levels, and the prognosis in patients with liver cirrhosis and refractory ascites who have undergone transjugular intrahepatic portosystemic shunt (TIPS). Child-Pugh and MELD scores have been extensively utilized for assessing the prognosis of cirrhosis, whereas serum Cys C levels serve as a potential biomarker reflecting renal function. The outcomes of this investigation may furnish valuable insights into the prognostic assessment of patients with liver cirrhosis and refractory ascites undergoing TIPS treatment.

Citation: Hu XG, Yang XX, Lu J, Li G, Dai JJ, Wang JM, Deng Y, Feng R. Correlation between serum markers and transjugular intrahepatic portosystemic shunt prognosis in patients with cirrhotic ascites. *World J Gastrointest Surg* 2024; 16(2): 481-490
URL: https://www.wjgnet.com/1948-9366/full/v16/i2/481.htm
DOI: https://dx.doi.org/10.4240/wjgs.v16.i2.481

INTRODUCTION

Cirrhosis is an end-stage condition characterized by liver damage that arises from multiple chronic liver diseases and constitutes a foremost contributor to worldwide morbidity and mortality[1,2]. With a diverse and complicated etiology, cirrhosis prevails across the globe, involving causative factors such as obesity, nonalcoholic fatty liver disease, excessive alcohol consumption, hepatitis B or C infections, autoimmune disorders, and cholestatic diseases[3,4]. Portal hypertension (PH) is a major complication of cirrhosis and manifests as severe clinical symptoms such as ascites, hepatic encephalopathy, and variceal bleeding[5]. Ascites is a highly prevalent complication associated with cirrhosis, and PH is the primary driving force behind the occurrence of ascites due to cirrhosis. Due to augmented intrahepatic vascular resistance resulting from structural liver damage, fibrosis, and endothelial dysfunction[6], 5%-10% of compensated cirrhosis patients develop ascites annually[7]. Presently, the predominant therapeutic modalities for managing Grade 1-3 ascites involve sodium restriction, diuretic administration, and large-volume abdominocentesis. Repeated large-volume abdominocentesis supplemented with albumin (Alb) is a first-line treatment method, while liver transplantation is recommended for refractory cases. Nevertheless, the presence of ascites signifies decompensated cirrhosis, and a considerable proportion of patients with ascites often have an adverse prognosis, marked by a median survival period of

approximately six months[8]. Consequently, there is an immediate and pressing need within clinical practice for efficacious interventions aimed at eradicating or fundamentally managing refractory ascites. Such interventions aim to alleviate clinical manifestations, enhance quality of life, and increase the survival rate[9].

A transjugular intrahepatic portosystemic shunt (TIPS) is a medical technique in which a stent is inserted through the jugular vein to establish an artificial conduit within the liver. This conduit redirects blood flow from the portal vein to the systemic circulation[10]. The TIPS is employed to treat PH complications by mitigating portal venous pressure[11]. In recent years, with advancements in TIPS technology, its indications have expanded, and it has found widespread application in the treatment of cirrhosis and its complications[12]. The "Guidelines for the Diagnosis and Treatment of Cirrhosis Ascites" also recommend TIPS as a second-line treatment for refractory ascites in cirrhosis patients[13]. Consequently, accurate postoperative prognosis assessment is pivotal. Nevertheless, at present, commonly adopted clinical biochemical markers such as Alb, sodium (Na^+), and serum creatinine (Scr) have limited predictive value, as Scr is easily influenced by protein intake and overall muscle mass. Furthermore, when Scr alterations are elicited by factors such as hyperbilirubinemia, prerenal azotemia, dietary intake modifications, and medication, Scr shows unfavorable diagnostic specificity, and all these factors can influence Scr levels in the absence of renal parenchyma damage[14]. Thus, novel biomarkers are essential for the assessment of liver cirrhosis patients with refractory ascites. Cystatin C (Cys C) is an endogenous marker of the glomerular filtration rate (GFR) that remains relatively stable and is minimally affected by factors such as sex, age, activity, and even inflammation. It can better reflect the extent of renal function impairment in patients[15]. Given that refractory ascites is often accompanied by severe renal function damage, monitoring Cys C levels for the assessment of post-TIPS prognosis in patients with liver cirrhosis and refractory ascites is feasible.

Therefore, this study focusing on patients with liver cirrhosis refractory ascites who underwent TIPS treatment aimed to explore the association between the prognosis after TIPS and the Child-Pugh and model for end-stage liver disease (MELD) scores, as well as Cys C levels. This investigation was conducted to identify more accurate prognostic indicators and refine treatment strategies for this specific patient cohort.

MATERIALS AND METHODS

Baseline data

Our research retrospectively evaluated 75 patients suffering from liver cirrhosis and refractory ascites who underwent TIPS treatment at our facility between August 2019 and August 2021. The criteria for inclusion were as follows: (1) Meeting the diagnostic criteria for patients with liver cirrhosis and refractory ascites as outlined in the "Diagnosis and Treatment Guidelines for Ascites and Related Complications in Cirrhosis"[16]; (2) Meeting the indications for TIPS surgery; and (3) Obtaining informed consent from both patients and their families for participation in the study. The exclusion criteria were as follows: (1) Concurrent malignancy; (2) Severe liver and kidney dysfunction; (3) Coagulation abnormalities; and (4) Incomplete clinical data. This study received approval from the institutional ethics committee, and comprehensive information, including the study's purpose and procedures, was conveyed to all patients and their families. Consent was obtained through the completion of informed consent forms, with the patients signifying their voluntary agreement to participate in the study.

Grouping

Combining passive and active follow-up methods, the patient follow-up encompassed diverse modalities, including home visits and telephonic verification. The follow-up concluded upon the occurrence of either death or liver transplant. The patients' survival outcomes were documented, and if a patient could not be reached for follow-up on three consecutive occasions (with an interval of more than half a month), they were classified as lost to follow-up. The conclusion of the follow-up occurred 2 years after the treatment. All affected patients were comprehensively recorded, and their follow-up outcomes were confirmed. All patients were followed up for a full duration of 2 years. The number of deaths and survivors at the 2-year mark was subjected to statistical analysis. Patients were assigned to a survival group (n = 45 patients) or a deceased group (n = 30 patients) based on their prognostic status (whether they survived or not).

Observation of indicators

Collection of baseline data: General information and past medical history, including sex, age, body mass index (BMI), systolic blood pressure, diastolic blood pressure, smoking history, and history of hypertension and CHD, were obtained from all enrolled subjects. The cohort of survivors consisted of 22 males and 23 females, ranging in age from 20 to 64 years, with a mean age of 42.3 ± 10.6 years. The deceased group comprised 17 males and 13 females aged between 22 and 65 years, with an average age of 43.1 ± 10.2 years. There were no statistically significant differences in age, sex, BMI, blood pressure, smoking history, hypertension, or coronary heart disease history between the two cohorts (all $P > 0.05$), suggesting comparability.

Detection of clinical indices: Comparisons of the serum glutamic oxalacetic transaminase [GOT or aspartate aminotransferase (AST)], glutamic pyruvic transaminase [GPT or alanine aminotransferase (ALT)], alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TBil), Alb, and Scr levels; blood urea nitrogen (BUN) level; Na^+ level; blood platelet count (PLT); prothrombin time (PT); and Cys C concentration were performed between the two groups. Specific methods: On the morning of the examination day, 5 mL of venous blood from the elbow was collected while the patients were in a fasting state. The blood samples were subjected to centrifugation at a speed of 3000 revolutions per minute and a centrifugal radius of 10 centimeters for a duration of 8 minutes. After the upper clear liquid was separated,

an automatic biochemical analyzer (produced by Beckman Coulter (China) Limited., model AU5800) was used to measure AST, ALT, ALP, GGT, TBil, Alb, Scr, BUN, Na+, PLT, PT, and Cys C levels in the serum. The reagent kits used were obtained from Shanghai Kehua Bio-Engineering Co., Ltd., and Shanghai Ruikang Biotechnology Co., Ltd. The procedures were carried out in alignment with SOP. All blood samples were tested within 2 h following collection.

Classic prognostic models: Calculations were made for the international normalized ratio (INR), Child-Pugh score, and MELD score as follows:

INR[17]: Calculated using the formula PT/international sensitivity index (ISI).

Child-Pugh scores[18] were calculated using the formula Alb (> 35 g/L, 1 point; 28-35 g/L, 2 points; < 28 g/L, 3 points); TBil (< 34 μmol, 1 point; 34-51 μmol, 2 points; > 51 μmol, 3 points); PT (≤ 14 s, 1 point; 15-17 s, 2 points; ≥ 18 s, 3 points); ascites (none, 1 point; easily removable, 2 points; difficult to remove, 3 points); and hepatic encephalopathy (none, 1 point; grade I-II, 2 points; grade III-IV, 3 points). The total score ranges from 1 to 15 points and is categorized as follows: Grade A (5-8 points), Grade B (9-11 points), or Grade C (12-15 points).

MELD scores[19] were calculated using the Formula 3.8 × In (TBil) (mg/dL) + 9.6 × In (Scr) (mg/dL) + 11.2In (INR) (mg/dL) + 6.4 × etiology, and the calculated outcome was rounded to the nearest integer.

Statistical analysis

The statistical analysis was performed with the assistance of SPSS 22.0 software. Measurement data are presented as "mean ± SD" and were analyzed using the *t* test, while enumeration data are presented as "%" and were evaluated *via* the χ^2 test. Spearman correlation analysis was used to evaluate the correlation between the Child-Pugh score, MELD score, and Cys C level and patient prognosis. Additionally, a multiple-factor analysis employing the Cox proportional hazard model was applied to ascertain the independent risk factors impacting the post-TIPS prognosis of liver cirrhosis patients with refractory ascites. The receiver operating characteristic (ROC) curve was used to evaluate the ability of the Cys C concentration, Child-Pugh grade, and MELD score to predict the prognosis for patients with liver cirrhosis and refractory ascites after surgery. When $P < 0.05$, the difference was considered to be statistically significant.

RESULTS

Comparison of clinical data between the two groups

After a 2-year follow-up, 30 deaths (40.00%) occurred among the 75 patients diagnosed with liver cirrhosis and refractory ascites who underwent TIPS treatment, 45 of whom (60.00%) survived. Within the deceased cohort, the AST (60.72 ± 14.09), ALT (45.19 ± 10.52), TBil (54.07 ± 16.76), Scr (72.21 ± 12.86), PT (17.83 ± 2.83), Cys C (2.43 ± 0.47), INR (1.84 ± 0.39), Child-Pugh (12.87 ± 1.29), and MELD (17.46 ± 2.98) values were higher than those in the survival cohort, for which AST (54.29 ± 11.57), ALT (121.90 ± 30.37), TBil (44.93 ± 13.64), Scr (66.04 ± 10.38), PT (16.12 ± 3.09), Cys C (1.68 ± 0.36), INR (1.57 ± 0.32), Child-Pugh (10.09 ± 1.45), and MELD (11.58 ± 2.34) values were recorded. Moreover, the Alb (24.67 ± 7.91) and Na^+ (126.74 ± 12.35) levels in the deceased group were lower than those in the survival group, for which Alb (29.52 ± 8.53) and Na^+ (136.24 ± 18.67) levels were recorded. The difference between the two cohorts was statistically significant ($P < 0.05$), as displayed in Table 1.

Spearman analysis of the correlation between patient prognosis and Child-Pugh score, MELD score, and Cys C concentration

Spearman analysis was used to investigate the correlation between prognosis and variables such as Child-Pugh score, MELD score, and Cys C. The results suggested that Child-Pugh ($r = 0.709$, $P < 0.05$), MELD ($r = 0.749$, $P < 0.05$), and Cys C ($r = 0.671$, $P < 0.05$) had moderate and high positive associations with prognosis, as displayed in Table 2.

Multiple factor analysis utilizing the Cox proportional hazard model for identifying independent risk factors influencing the prognosis for patients with refractory ascites due to liver cirrhosis following TIPS

The findings of the multifactor analysis employing the Cox proportional hazard model showed that the independent risk factors for post-TIPS prognosis in patients with liver cirrhosis and refractory ascites were Cys C (hazard ratio (HR): 3.802; 95%CI: 1.313-11.015), Child-Pugh scores (HR: 3.030; 95%CI: 1.858-4.943), and MELD scores (HR: 1.222; 95%CI: 1.073-1.393; Table 3).

ROC analysis for single risk factors predicting the post-TIPS prognosis of patients with refractory ascites due to liver cirrhosis

The findings of the ROC analysis revealed that the classic prognostic models based on the Child-Pugh and MELD scores exhibited marginally superior diagnostic efficacy in predicting the post-TIPS prognosis in patients with liver cirrhosis and refractory ascites. For the Child-Pugh score, the sensitivity and specificity were 90% and 84.244%, respectively, with an area under the curve (AUC) of 0.919 and an optimal cutoff value of 11.5 points. For the MELD score, the sensitivity and specificity were 86.67% and 82.22%, respectively, with an AUC of 0.934 and an optimal cutoff value of 13.5 points. In contrast, Cys C exhibited a slight decrease in diagnostic efficiency for predicting post-TIPS prognosis in patients with liver cirrhosis and refractory ascites, with a sensitivity and specificity of 83.33% and 82.22%, respectively; an AUC of 0.883; and an optimal cutoff value of 1.95 mg/L (Table 4 and Figure 1).

Table 1 Comparison of clinical data between the two groups

Group		Survival group (n = 45 cases)	Deceased group (n = 30 cases)	t/χ^2	P value
Age (yr)		51.42 ± 7.28	53.25 ± 7.09	1.078	0.285
Sex	Male	26	16	0.144	0.704
	Female	19	14		
Combined background disease	Presence	15	12	0.347	0.556
	Absence	30	18		
Family history	Presence	4	5	1.031	0.310
	Absence	41	25		
Smoking history	Presence	12	11	0.847	0.358
	Absence	33	19		
Drinking history	Presence	10	10	1.136	0.286
	Absence	35	20		
AST (U/L)		54.29 ± 11.57	60.72 ± 14.09	2.160	0.034
ALT (U/L)		40.31 ± 9.86	45.19 ± 10.52	2.044	0.045
ALP (U/L)		121.90 ± 30.37	129.74 ± 32.37	1.067	0.290
GGT (U/L)		64.86 ± 16.25	70.38 ± 18.39	1.367	0.176
Tbil (μmol/L)		44.93 ± 13.64	54.07 ± 16.76	2.593	0.012
Alb (g/L)		29.52 ± 8.53	24.67 ± 7.91	2.482	0.015
Scr (μmol/L)		66.04 ± 10.38	72.21 ± 12.86	2.290	0.025
BUN (μmol/L)		7.23 ± 2.07	7.41 ± 2.18	0.361	0.719
Na^+ (mmol/L)		136.24 ± 18.67	126.74 ± 12.35	2.450	0.017
PLT ($\times 10^9$/L)		60.03 ± 12.47	56.42 ± 10.19	1.318	0.192
PT (s)		16.12 ± 3.09	17.83 ± 2.83	2.427	0.018
Cys C (mg/L)		1.68 ± 0.36	2.43 ± 0.47	7.813	0.000
INR		1.57 ± 0.32	1.84 ± 0.39	3.278	0.002
Child-Pugh score (points)		10.09 ± 1.45	12.87 ± 1.29	8.494	0.000
MELD score (points)		11.58 ± 2.34	17.46 ± 2.98	9.547	0.000

MELD: Model for end-stage liver disease; Cys C: Cystatin C; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; TBil: Total bilirubin; PT: Prothrombin time; PLT: Blood platelet count; BUN: Blood urea nitrogen; Alb: Albumin; Scr: Serum creatinine; INR: International normalized ratio.

Table 2 Spearman analysis of the correlation between prognosis and Child-Pugh score, model for end-stage liver disease score, and cystatin C level

Indicator	Child-Pugh scores		MELD scores		Cys C	
	r	P value	r	P value	r	P value
Prognosis	0.709	0.000	0.749	0.000	0.670	0.000

MELD: Model for end-stage liver disease; Cys C: Cystatin C.

Table 3 Multiple factor analysis utilizing the Cox proportional hazard model for identifying independent risk factors influencing the prognosis of patients with liver cirrhosis and refractory ascites following transjugular intrahepatic portosystemic shunt

Factor	B	Sb	Wald χ^2	*P* value	HR (95%CI)
AST	-0.022	0.017	1.627	0.202	0.978 (0.946-1.012)
ALT	0.041	0.027	2.320	0.128	1.042 (0.988-1.099)
TBil	-0.017	0.016	1.179	0.278	0.983 (0.953-1.014)
Alb	-0.012	0.033	0.131	0.717	0.988 (0.927-1.054)
Scr	-0.042	0.023	3.243	0.072	0.959 (0.916-1.004)
Na^+	-0.028	0.021	1.766	0.184	0.972 (0.933-1.013)
PT	0.001	0.095	0.000	0.991	1.001 (0.831-1.206)
Cys C	1.336	0.543	6.057	0.014	3.802 (1.313-11.015)
INR	1.282	0.714	3.228	0.072	3.604 (0.890-14.597)
Child-Pugh scores	1.109	0.250	19.723	0.000	3.030 (1.858-4.943)
MELD scores	0.201	0.067	9.099	0.003	1.222 (1.073-1.393)

MELD: Model for end-stage liver disease; Cys C: Cystatin C; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; TBil: Total bilirubin; PT: Prothrombin time; PLT: Blood platelet count; BUN: Blood urea nitrogen; Alb: Albumin; Scr: Serum creatinine; INR: International normalized ratio.

Table 4 Receiver operating characteristic analysis for single risk factors predicting the post-transjugular intrahepatic portosystemic shunt prognosis of patients with refractory ascites due to liver cirrhosis

Risk factor	ROC curve			Optimal cutoff value	Sensitivity (%)	Specificity (%)
	AUC	95%CI	*P* value			
Cys C	0.883	0.803-0.963	0.000	1.95 mg/L	83.33 (25/30)	82.22 (37/45)
Child-Pugh scores	0.919	0.856-0.981	0.000	11.50 points	90.00 (27/30)	84.44 (38/45)
MELD scores	0.934	0.879-0.988	0.000	13.50 points	86.67 (26/30)	82.22 (37/45)

ROC: Receiver operating characteristic; MELD: Model for end-stage liver disease; Cys C: Cystatin C; AUC: Area under the curve.

DISCUSSION

The primary initiating factor for refractory ascites is liver cirrhosis with PH. This condition can cause bacterial translocation, vascular dilation, renal perfusion insufficiency, and water-sodium retention, eventually resulting in ascites and progression to refractory ascites. According to current and international guidelines, liver transplantation is an efficacious treatment. Nevertheless, in light of the scarcity of available donor livers, TIPS placement is advocated as a viable alternative. It artificially establishes an intrahepatic shunt connecting the hepatic vein and portal vein on the liver parenchyma, effectively mitigating portal venous pressure to improve hemodynamics and kidney function[20,21]. Considering that patients with liver cirrhosis and refractory ascites progress to the decompensated stage, characterized by a more unfavorable prognosis when juxtaposed with compensated cirrhosis patients[22], individuals undergoing TIPS surgery are susceptible to a spectrum of complications. These complications may result in frequent readmissions and are inextricably linked to poor prognosis. For instance, as indicated by preceding studies, among all decompensated cirrhosis patients undergoing TIPS surgery, 2997 individuals (10.69%) died during hospitalization. Moreover, among patients who were readmitted within 30 days after discharge and who underwent TIPS surgery during their readmission, 405 (6.05%) died in the hospital[23]. The elevated mortality rate observed in patients with liver cirrhosis refractory ascites following TIPS surgery can be ascribed to a myriad of contributing factors. A study by Kumada *et al*[24] demonstrated that age (aHR = 2.692) is an independent risk factor for nonliver-related mortality during the decompensation phase of cirrhosis, with male sex (aHR = 3.045) having an impact on liver-related mortality. Another study by Balcar *et al*[25] revealed that when cirrhosis patients with Grade 3 ascites (*i.e.*, refractory ascites) have MELD scores ≥ 15, there is a greater risk of recurrent decompensation (SHR = 2.18) and mortality (SHR = 1.89). Nevertheless, in the classic prognostic models constructed in the past, Child-Pugh scores weighted all 5 dimensions equally, leading to potential overestimation or underestimation in the comprehensive analysis. Additionally, the assessment of ascites and hepatic encephalopathy is subjective, and the calculation of the MELD score is complex, with sensitivity and specificity being somewhat reduced when the score is < 20[26]. In our investigation, we performed routine follow-up assessments of patients in this cohort

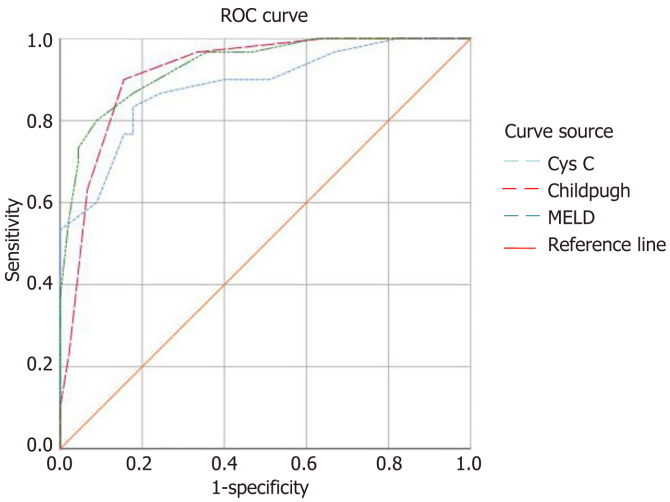

Figure 1 Receiver operating characteristic curve analysis of single risk factors for predicting post-transjugular intrahepatic portosystemic shunt prognosis in liver cirrhosis patients with refractory ascites. The diagonal is generated by binding value. ROC: Receiver operating characteristic; MELD: Model for end-stage liver disease; Cys C: Cystatin C.

over a span of 2 years, meticulously documenting the incidence of mortality. A 2-year mortality rate of 40.0% was observed among liver cirrhosis patients with refractory ascites subsequent to TIPS surgery. This rate differs significantly from the 10.69% reported by Khan *et al*[23]. The variance may be attributed to disparities in the patient population, duration of follow-up, and treatment modalities. Consequently, the active pursuit of biomarkers for liver cirrhosis patients with refractory ascites who have undergone TIPS surgery holds significant value in determining their prognosis. Further exploration of clinically reliable and practical specific biomarkers for the early prediction of the post-TIPS prognosis in patients with liver cirrhosis and refractory ascites has become a current research focal point.

Cys C, characterized by its low molecular weight and nonglycated nature, is stably synthesized by the body's nucleus cells. Its metabolic processes are predominantly confined to the renal system, wherein it undergoes free filtration in the glomeruli and subsequent reabsorption and breakdown in the proximal tubules. Cys C synthesis remains relatively steady and is scarcely influenced by factors such as sex, age, or activity. Initially, the NRS-2002 was used to assess early renal function impairment in patients[27]. Several previous investigations have revealed that the measurement of Cys C is a valuable instrument for the timely detection of moderate renal dysfunction, especially in individuals with cirrhosis (especially those in Child-Pugh class C) or female patients[15,28-30]. A study by Seo *et al*[31] demonstrated that Cys C levels are an independent predictor of mortality in cirrhosis patients with ascites, whereas Scr levels are not. Notably, a study by Torner *et al*[32] demonstrated for the first time that in TIPS patients, creatinine is a better predictor of mortality in males, while Cys C is a better predictor of mortality in females. Nevertheless, there is a significant dearth of research on Cys C in patients who have undergone TIPS treatment. The Child-Pugh score is a commonly applied clinical grading criterion for quantitatively assessing liver reserve function in patients with cirrhosis. The MELD score is a recognized indicator of cirrhosis severity and serves as a predictive factor for the incidence and mortality rate among patients undergoing TIPS and liver transplantation allocation[33]. Given this background, we explored the correlation of Cys C levels, Child-Pugh scores, and MELD scores with the prognosis of liver cirrhosis patients with refractory ascites post-TIPS. Our observations showed that subsequent to a 2-year follow-up, compared to those in the survival cohort, the deceased cohort had heightened Cys C levels. Spearman analysis revealed moderate to high positive correlations between the Child-Pugh score, MELD score, and Cys C concentration and patient prognosis. The Child-Pugh and MELD scores are classic prognostic models, which suggest that the Cys C concentration can be used to evaluate the prognosis of patients with liver cirrhosis and refractory ascites following TIPS to some extent. In light of these findings, our research harnessed the Cox proportional hazard model for multiple-factor analysis, suggesting that the independent risk factors impacting the prognosis of liver cirrhosis patients with refractory ascites after TIPS were Cys C, the Child-Pugh score, and the MELD score. Additionally, we assessed the predictive value of Cys C through receiver operating characteristic (ROC) curve analysis. The outcomes revealed that Cys C had a slightly lower diagnostic efficiency for predicting the prognosis of liver cirrhosis patients with refractory ascites post-TIPS, with sensitivity and specificity values of 83.33% and 82.22%, respectively, an AUC value of 0.883, and an optimal cutoff value of 1.95 mg/L. Although it exhibited slightly diminished diagnostic efficacy compared to Child-Pugh and MELD scores, it furnished an important direction for improving prognostic models. This finding is similar to that of a study by Suksamai *et al*[34], which showed that Cys C > 1.45 mg/L could predict the 90-day mortality rate in patients with cirrhosis and complications quite well (HR: 2.04, 95%CI: 1.01-4.14), with sensitivity and specificity values of 66.7% and 68.4%, respectively. The variance in findings could be ascribed to the fact that our study included patients with liver cirrhosis refractory ascites who had more severe conditions than those in the abovementioned study involving patients with cirrhosis and complications. Moreover, our investigation featured a 2-year follow-up duration, utilizing mortality as the primary endpoint. This finding diverges from that of previously cited research, which focused on the 90-day mortality rate. Consequently, Cys C levels were higher, and the prognosis was much poorer. Nevertheless, there are several limitations in our study: (1) Conducted as a retrospective study, our research is characterized by a relatively modest sample size comprising only 75 patients. This inherent limi-

tation has the potential to introduce certain biases into the conclusions drawn from the study; and (2) Our study population consisted of patients with liver cirrhosis combined with refractory ascites who underwent TIPS rather than those with other complications of liver cirrhosis.

CONCLUSION

In summary, for patients with liver cirrhosis and refractory ascites with a poor prognosis after TIPS, elevated serum Cys C levels were observed. These levels displayed a moderate to high positive correlation with classic prognostic models, such as the Child-Pugh and MELD scores. The Cox proportional hazard model confirmed that the serum Cys C concentration was an independent risk factor influencing the prognosis in liver cirrhosis patients with refractory ascites post-TIPS (HR = 3.802; 95%CI: 1.313-11.015). Given their convenience, minimal susceptibility to sex, age, activity, and inflammation, as well as their ability to furnish reliable data, measurements of Cys C can potentially function as specific inflammatory biomarkers for the assessment of prognosis in individuals affected by these medical conditions. Furthermore, ROC curve analysis validated the value of the serum Cys C concentration in assessing the prognosis of liver cirrhosis patients with refractory ascites post-TIPS, with an optimal cutoff value of 1.95 mg/L. This has remarkable guiding implications for follow-up and treatment. However, the utility of predictive models based on Cys C needs confirmation in prospective large-scale studies.

ARTICLE HIGHLIGHTS

Research background

The transjugular intrahepatic portosystemic shunt (TIPS) is a frequently employed interventional technique for the management of hepatic ascites, yet uncertainties persist regarding its prognosis. Serum marker levels may play a crucial role in predicting the prognosis of patients with hepatic ascites who are undergoing TIPS procedures.

Research motivation

Currently, there is a lack of comprehensive research on the correlation between serum marker levels and the prognosis for TIPSs in hepatic ascites patients, resulting in a limited understanding of this topic. Consequently, the purpose of this study was to comprehensively explore the associations between various serum markers and the prognosis in individuals with hepatic ascites who underwent TIPS, with the aim of enhancing the precision of prognostic assessment and guiding treatment strategies.

Research objectives

This study aimed to investigate the associations between Child-Pugh score, model for end-stage liver disease (MELD) score, serum cystatin C (Cys C) level, and post-TIPS prognosis in patients with liver cirrhosis refractory ascites.

Research methods

We conducted a retrospective study involving 75 patients with decompensated liver cirrhosis and refractory ascites, all of whom underwent TIPS at our institution from August 2019 to August 2021. Over a two-year period, comprehensive follow-up assessments were undertaken, and patient outcomes were meticulously recorded. Clinical data, including Child-Pugh and MELD scores, were systematically collected. Spearman correlation analysis was used to evaluate the associations between the Child-Pugh score, MELD score, and Cys C level. The Cox proportional hazards model was used to identify independent risk factors influencing patient prognosis. Receiver operating characteristic curves were generated to assess the ability of Cys C levels, Child-Pugh scores, and MELD scores to predict the prognosis subsequent to TIPS treatment.

Research results

After 2 years of TIPS treatment, 40.00% of the 75 patients with refractory ascites due to liver cirrhosis passed away. Increased aspartate aminotransferase, alanine aminotransferase, total bilirubin, serum creatinine (Scr), prothrombin time, Cys C, international normalized ratio, Child-Pugh, and MELD scores were observed in the deceased group, while albumin and Na+ levels decreased ($P < 0.05$). The Child-Pugh score, MELD score, and Cys C concentration were identified as independent risk factors for the prognosis of TIPS treatment in patients with refractory ascites due to liver cirrhosis. Cys C showed slightly lower predictive accuracy for prognosis, with a sensitivity of 83.33% and specificity of 82.22%. The area under the curve was 0.883, with a cutoff value of 1.95 mg/L.

Research conclusions

Monitoring the serum Cys C concentration holds great value in assessing the prognosis in patients with refractory ascites due to liver cirrhosis after TIPS treatment. Compared to the use of Scr levels, predictive models based on serum Cys C levels are more beneficial for evaluating the condition and prognosis of patients with ascites due to cirrhosis.

Research perspectives

This study provides evidence of the correlation between serum biomarkers and the prognosis of patients undergoing TIPS, which may serve as a prognostic indicator. Nevertheless, additional validation and extension of the relationship between serum biomarkers and TIPS prognosis necessitate further inquiry. This entails conducting larger-sample clinical trials and exploring additional factors that may influence prognosis.

FOOTNOTES

Author contributions: Hu XG and Feng R designed the study; Yang XX and Feng R wrote the manuscript; Hu XG, Yang XX, Deng Y, Li G, and Dai JJ performed the experiments; Lu J, Wang JM, Deng Y, and Feng R analyzed the data; and all the authors read and approved the final manuscript.

Institutional review board statement: The study was approved by the Ethics Committee of Affiliated Jinhua Hospital, Zhejiang University School of Medicine.

Informed consent statement: The data used in the study were not involved in the patients' privacy information, and all patient data obtained, recorded, and managed only used for this study, without any harm to the patient. So the informed consent was waived by the Ethics Committee of Affiliated Jinhua Hospital, Zhejiang University School of Medicine.

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

Data sharing statement: No additional data are available.

Country/Territory of origin: China

ORCID number: Rui Feng 0000-0001-8757-2607.

S-Editor: Yan JP
L-Editor: A
P-Editor: Zhang YL

REFERENCES

1 **Wilson R**, Williams DM. Cirrhosis. *Med Clin North Am* 2022; **106**: 437-446 [PMID: 35491064 DOI: 10.1016/j.mcna.2021.12.001]
2 **Zhou WC**, Zhang QB, Qiao L. Pathogenesis of liver cirrhosis. *World J Gastroenterol* 2014; **20**: 7312-7324 [PMID: 24966602 DOI: 10.3748/wjg.v20.i23.7312]
3 **Bajaj JS**, Kamath PS, Reddy KR. The Evolving Challenge of Infections in Cirrhosis. *N Engl J Med* 2021; **384**: 2317-2330 [PMID: 34133861 DOI: 10.1056/NEJMra2021808]
4 **Ginès P**, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet* 2021; **398**: 1359-1376 [PMID: 34543610 DOI: 10.1016/S0140-6736(21)01374-X]
5 **Karagiannakis DS**, Voulgaris T, Siakavellas SI, Papatheodoridis GV, Vlachogiannakos J. Evaluation of portal hypertension in the cirrhotic patient: hepatic vein pressure gradient and beyond. *Scand J Gastroenterol* 2018; **53**: 1153-1164 [PMID: 30345856 DOI: 10.1080/00365521.2018.1506046]
6 **Tonon M**, Piano S. Cirrhosis and Portal Hypertension: How Do We Deal with Ascites and Its Consequences. *Med Clin North Am* 2023; **107**: 505-516 [PMID: 37001950 DOI: 10.1016/j.mcna.2022.12.004]
7 **Adebayo D**, Neong SF, Wong F. Refractory Ascites in Liver Cirrhosis. *Am J Gastroenterol* 2019; **114**: 40-47 [PMID: 29973706 DOI: 10.1038/s41395-018-0185-6]
8 **Jeong SW**. [Ascites]. *Korean J Gastroenterol* 2018; **72**: 49-55 [PMID: 30145856 DOI: 10.4166/kjg.2018.72.2.49]
9 **Larrue H**, Vinel JP, Bureau C. Management of Severe and Refractory Ascites. *Clin Liver Dis* 2021; **25**: 431-440 [PMID: 33838859 DOI: 10.1016/j.cld.2021.01.010]
10 **Rajesh S**, George T, Philips CA, Ahamed R, Kumbar S, Mohan N, Mohanan M, Augustine P. Transjugular intrahepatic portosystemic shunt in cirrhosis: An exhaustive critical update. *World J Gastroenterol* 2020; **26**: 5561-5596 [PMID: 33088154 DOI: 10.3748/wjg.v26.i37.5561]
11 **Parker R**. Role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension. *Clin Liver Dis* 2014; **18**: 319-334 [PMID: 24679497 DOI: 10.1016/j.cld.2013.12.004]
12 **Zhang JB**, Chen J, Zhou J, Wang XM, Chen S, Chu JG, Liu P, Ye ZD. Systematic review and meta-analysis of trans-jugular intrahepatic portosystemic shunt for cirrhotic patients with portal vein thrombosis. *World J Clin Cases* 2021; **9**: 5179-5190 [PMID: 34307565 DOI: 10.12998/wjcc.v9.i19.5179]
13 **Angeli P**. The first Chinese guidelines on the Management of Ascites and its Related Complications in Cirrhosis: a great goal for a great country. *Hepatol Int* 2019; **13**: 395-398 [PMID: 31313026 DOI: 10.1007/s12072-019-09961-4]

14 **Waikar SS**, Betensky RA, Emerson SC, Bonventre JV. Imperfect gold standards for kidney injury biomarker evaluation. *J Am Soc Nephrol* 2012; **23**: 13-21 [PMID: 22021710 DOI: 10.1681/ASN.2010111124]

15 **Abd El Wahab AM**, Awadeen A, Mansour MM, Shemies R. The diagnostic and prognostic utility of serum cystatin C and angiopoietin 2 in patients with liver cirrhosis complicated by acute kidney injury. *Ther Apher Dial* 2023; **27**: 419-427 [PMID: 36181409 DOI: 10.1111/1744-9987.13936]

16 **Chinese Society of Hepatology**; Chinese Medical Association, Xu X, Duan Z, Ding H, Li W, Jia J, Wei L, Linghu E, Zhuang H. Chinese guidelines on the management of ascites and its related complications in cirrhosis. *Hepatol Int* 2019; **13**: 1-21 [PMID: 30656520 DOI: 10.1007/s12072-018-09923-2]

17 **Hirsh J**, Poller L. The international normalized ratio. A guide to understanding and correcting its problems. *Arch Intern Med* 1994; **154**: 282-288 [PMID: 8297194 DOI: 10.1001/archinte.154.3.282]

18 **Favaloro EJ**. Optimizing the Verification of Mean Normal Prothrombin Time (MNPT) and International Sensitivity Index (ISI) for Accurate Conversion of Prothrombin Time (PT) to International Normalized Ratio (INR). *Methods Mol Biol* 2017; **1646**: 59-74 [PMID: 28804818 DOI: 10.1007/978-1-4939-7196-1_4]

19 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

20 **Singh V**, De A, Mehtani R, Angeli P, Maiwall R, Satapathy S, Singal AK, Saraya A, Sharma BC, Eapen CE, Rao PN, Shukla A, Shalimar, Choudhary NS, Alcantara-Payawal D, Arora V, Aithal G, Kulkarni A, Roy A, Shrestha A, Mamun Al Mahtab, Niriella MA, Siam TS, Zhang CQ, Huei LG, Yu ML, Roberts SK, Peng CY, Chen T, George J, Wong V, Yilmaz Y, Treeprasertsuk S, Kurniawan J, Kim SU, Younossi ZM, Sarin SK. Asia-Pacific association for study of liver guidelines on management of ascites in liver disease. *Hepatol Int* 2023; **17**: 792-826 [PMID: 37237088 DOI: 10.1007/s12072-023-10536-7]

21 **Aithal GP**, Palaniyappan N, China L, Härmälä S, Macken L, Ryan JM, Wilkes EA, Moore K, Leithead JA, Hayes PC, O'Brien AJ, Verma S. Guidelines on the management of ascites in cirrhosis. *Gut* 2021; **70**: 9-29 [PMID: 33067334 DOI: 10.1136/gutjnl-2020-321790]

22 **Lin CL**, Tseng KC, Chen KY, Liao LY, Kao JH. Factors predicting outcomes of hepatitis B-related cirrhosis patients with long-term antiviral therapy. *J Formos Med Assoc* 2020; **119**: 1483-1489 [PMID: 32653388 DOI: 10.1016/j.jfma.2020.07.003]

23 **Khan A**, Maheshwari S, Gupta K, Naseem K, Chowdry M, Singh S. Rate, reasons, predictors, and burden of readmissions after transjugular intrahepatic portosystemic shunt placement. *J Gastroenterol Hepatol* 2021; **36**: 775-781 [PMID: 32710679 DOI: 10.1111/jgh.15194]

24 **Kumada T**, Toyoda H, Yasuda S, Miyake N, Ito T, Tanaka J. Long-term prognosis with or without nucleot(s)ide analogue therapy in hepatitis B virus-related decompensated cirrhosis. *J Viral Hepat* 2021; **28**: 508-516 [PMID: 33306854 DOI: 10.1111/jvh.13457]

25 **Balcar L**, Tonon M, Semmler G, Calvino V, Hartl L, Incicco S, Jachs M, Bauer D, Hofer BS, Gambino CG, Accetta A, Brocca A, Trauner M, Mandorfer M, Piano S, Reiberger T; Baveno Cooperation: an EASL consortium. Risk of further decompensation/mortality in patients with cirrhosis and ascites as the first single decompensation event. *JHEP Rep* 2022; **4**: 100513 [PMID: 35845294 DOI: 10.1016/j.jhepr.2022.100513]

26 **Torp N**, Israelsen M, Madsen B, Lutz P, Jansen C, Strassburg C, Mortensen C, Knudsen AW, Sorensen GL, Holmskov U, Schlosser A, Thiele M, Trebicka J, Krag A. Level of MFAP4 in ascites independently predicts 1-year transplant-free survival in patients with cirrhosis. *JHEP Rep* 2021; **3**: 100287 [PMID: 34041469 DOI: 10.1016/j.jhepr.2021.100287]

27 **Shlipak MG**, Inker LA, Coresh J. Serum Cystatin C for Estimation of GFR. *JAMA* 2022; **328**: 883-884 [PMID: 35939309 DOI: 10.1001/jama.2022.12407]

28 **Mindikoglu AL**, Opekun AR, Mitch WE, Magder LS, Christenson RH, Dowling TC, Weir MR, Seliger SL, Howell CD, Raufman JP, Rana A, Goss JA, Khaderi SA, Vierling JM. Cystatin C Is a Gender-Neutral Glomerular Filtration Rate Biomarker in Patients with Cirrhosis. *Dig Dis Sci* 2018; **63**: 665-675 [PMID: 29392554 DOI: 10.1007/s10620-017-4897-z]

29 **Randers E**, Ivarsen P, Erlandsen EJ, Hansen EF, Aagaard NK, Bendtsen F, Vilstrup H. Plasma cystatin C as a marker of renal function in patients with liver cirrhosis. *Scand J Clin Lab Invest* 2002; **62**: 129-134 [PMID: 12004928 DOI: 10.1080/00365510252753611753]

30 **Gerbes AL**, Gülberg V, Bilzer M, Vogeser M. Evaluation of serum cystatin C concentration as a marker of renal function in patients with cirrhosis of the liver. *Gut* 2002; **50**: 106-110 [PMID: 11772976 DOI: 10.1136/gut.50.1.106]

31 **Seo YS**, Park SY, Kim MY, Kim SG, Park JY, Yim HJ, Jang BK, Park SH, Kim JH, Suk KT, Kim JD, Kim TY, Cho EY, Lee JS, Jung SW, Jang JY, An H, Tak WY, Baik SK, Hwang JS, Kim YS, Sohn JH, Um SH. Serum cystatin C level: An excellent predictor of mortality in patients with cirrhotic ascites. *J Gastroenterol Hepatol* 2018; **33**: 910-917 [PMID: 28910501 DOI: 10.1111/jgh.13983]

32 **Torner M**, Mangal A, Scharnagl H, Jansen C, Praktiknjo M, Queck A, Gu W, Schierwagen R, Lehmann J, Uschner FE, Graf C, Strassburg CP, Fernandez J, Stojakovic T, Woitas R, Trebicka J. Sex specificity of kidney markers to assess prognosis in cirrhotic patients with TIPS. *Liver Int* 2020; **40**: 186-193 [PMID: 31448496 DOI: 10.1111/liv.14230]

33 **Bayona Molano MDP**, Barrera Gutierrez JC, Landinez G, Mejia A, Haskal ZJ. Updates on the Model for End-Stage Liver Disease Score and Impact on the Liver Transplant Waiting List: A Narrative Review. *J Vasc Interv Radiol* 2023; **34**: 337-343 [PMID: 36539154 DOI: 10.1016/j.jvir.2022.12.029]

34 **Suksamai A**, Chaiprasert A, Chirapongsathorn S. Serum cystatin C as a predictor of 90-day mortality among patients admitted with complications of cirrhosis. *JGH Open* 2021; **5**: 607-613 [PMID: 34013062 DOI: 10.1002/jgh3.12543]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com