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Retrospective Study

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

Hu XG *et al.* Serum markers and TIPS prognosis in cirrhotic ascites

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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

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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 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 cystatin 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.

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. ⁵ 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 $3.8 \times \ln(\text{TBil}) (\text{mg/dL}) + 9.6 \times \ln(\text{Scr}) (\text{mg/dL}) + 11.2 \ln(\text{INR}) (\text{mg/dL}) + 6.4 \times \text{etiology}$, 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

² 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.

¹ *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 ¹ 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; ⁶ 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).

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 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 limitation 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.

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