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Sex specificity of kidney markers to assess prognosis in cirrhotic patients with TIPS

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Abstract

Background & Aims: Renal function assessed by creatinine is a key prognostic factor in cirrhotic patients. However, creatinine is influenced by several factors, rendering interpretation difficult in some situations. This is especially important in early stages of renal dysfunction where renal impairment might not be accompanied by an increase in creatinine. Other parameters, such as cystatin C (CysC) and beta-trace protein (BTP), have been evaluated to fill this gap. However, none of these studies have considered the role of the patient's sex. The present study analysed CysC and BTP to evaluate their prognostic value and differentiate them according to sex.

Patients and methods: CysC and BTP were measured in 173 transjugular intrahepatic portosystemic shunt (TIPS)-patients from the NEPTUN-STUDY(NCT03628807) and analysed their relationship with mortality and sex. Propensity score for age, MELD, etiology and TIPS indication was used.

Results: Cystatin C and BTP showed excellent correlations with creatinine values at baseline and follow-up. CysC was an independent predictor of overall mortality

Abbreviations: ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; BTP, beta-trace protein; CysC, cystatin c; EH, hepatic encephalopathy; HRS, hepatorenal syndrome; MELD, model for end-stage liver disease; ROC, receiver operating characteristics; TIPS, transjugular intrahepatic portosystemic shunt.

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Stojakovic, Woitas and Trebicka shared last authorship.

(HR = 1.66(1.33-2.06)) with an AUC of 0.75 and identified a cut-off of 1.55 mg/L in the whole cohort. Interestingly, CysC was significantly lower in females, also after propensity score matching. In males, the only independent predictor was the creatinine level (HR = 1.54(1.25-1.58)), while in females CysC levels independently predicted mortality (HR = 3.17(1.34-7.52)).

Conclusion: This study demonstrates for the first time that in TIPS-patients creatinine predicts mortality in males better than in females, whereas CysC is a better predictor of mortality in females. These results may influence future clinical decisions on therapeutic options for example, allocation for liver transplantation in TIPS-patients.

KEYWORDS

beta-trace protein, cirrhosis, cystatin C, portal hypertension, renal function

1 | INTRODUCTION

Chronic liver injury leads to cirrhosis with portal hypertension, which is associated with complications, such as refractory ascites and variceal bleeding,[1] both of which are directly linked to the degree of portal hypertension. Decompression of portal hypertension by placing a transjugular intrahepatic portosystemic shunt (TIPS) is a very effective way to control these complications.[2,3] While the prevention of rebleeding is because of the numerical decrease in portal pressure,[4] the treatment of refractory ascites is a result of the improvement in effective blood volume and improved renal perfusion and function.[5,6] In fact, renal function is one of the key prognostic factors in cirrhosis and its daily basic estimation is made by measuring creatinine levels. Creatinine has also been used in the calculation of the model for end-stage liver disease (MELD) score, which was designed to estimate 3-month survival after TIPS,[7] and now is applied in many settings, for example, for organ allocation in liver transplantation.[8] However, there is growing evidence that creatinine is not the best parameter to estimate kidney function and thus survival in female patients.[9-11]

In recent studies, the roles of cystatin C (CysC) and beta-trace-protein (BTP) have been investigated, not only as parameters to reflect renal function, but also for prognostic purposes.[12,13] CysC, but not BTP, has been shown to assess not only renal function,[11] but also survival in patients with acute-on-chronic liver failure, as well as in patients developing acute kidney injury (AKI).[12] Recent reports have highlighted that muscle mass is relevant and that CysC is less prone to be influenced by muscle mass. However, neither the influence of sex specificity on CysC nor on BTP levels and its effect on outcome has been investigated to date.

The present work aims to define the sex specificity prognostic value of CysC and BTP in patients with cirrhosis and TIPS.

Key points

- In cirrhosis, kidney function predicts survival.
- In a specific group of patients, receiving transjugular intrahepatic portosystemic shunt, it seems that sex influences the markers, which predict survival: in male creatinine and in female cystatin C.

2 | PATIENTS AND METHODS

2.1 | Patient collectives and data acquisition

This study investigates 173 cirrhotic patients receiving TIPS in the Department of Internal Medicine I, University Clinic Bonn, Germany. The patients were divided into two cohorts. Cohort I consisted of 106 patients, who received TIPS between 1997 and 2013, cohort II included 67 patients, in whom TIPS was inserted between 2014 and 2015. As the two cohorts were not significantly different, all patients were analysed together. All patients received a structured follow-up period after TIPS as highlighted in the Non-invasive Evaluation Program for TIPS and Follow Up Network (NEPTUN) study (NCT03628807). Of note, patients with chronic kidney disease and hepatocellular carcinoma were not included in the TIPS-programme and thereby in this study. The first visit was 7 days after TIPS as inpatient, then after 1 month, 2 months and thence every 3 months as outpatient. About 26 patients were lost to follow-up and were not included in the survival analysis. Biochemical blood analyses were performed using standard tests. Hepatorenal syndrome was diagnosed according to the recent EASL-guidelines.[14] The local ethics committee of the University of Bonn approved the study (029/13), and all patients signed an informed written consent in accordance with the Helsinki Declaration for the procedures they underwent.

2.2 | Determination of cystatin C and BTP

Samples were collected and frozen at −70°C at the local institution. Serum cystatin C and BTP were measured at the Clinical Insitute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Austria. Cystatin C and BTP were determined using particle-enhanced immuno-nephelometric assays (N Latex Cystatin C, N

Latex BTP assay, Siemens Healthcare GmbH, Marburg, Germany) at a Behring nephelometer II. The interassay coefficients of variation (CV) for cystatin C were 5.1% and 4.9% at concentrations of 0.97 and 1.9 mg/L (72.7 and 142.3 nmol/L) respectively. Serum cystatin C has been reported to be robust to multiple freeze-thaw cycles. The interassay CVs for BTP were 3.5% and 3.1% at concentrations of 1.02 and 1.83 mg/L respectively.

2.3 | Statistical analysis

Descriptive statistics were computed for all variables. Non-parametric testing was used to compare different groups when suitable. Paired non-parametric testing was used to compare data before and after TIPS procedure on the same patients. Correlation of metric variables was performed using Spearman's correlation.

To account for the lack of imbalance at baseline between males and females a (1:1), propensity score matching of the entire cohort for males and females was performed adjusted for age, MELD, etiology and TIPS indication with a maximum propensity score distance (caliper) of 0.5. Sixty-four males and 64 females were included for further analysis.

The prognostic value and selection of cut-off values of cystatin C was analysed using receiver operating characteristics (ROC) with overall survival as end point. Kaplan-Meier curve with log-rank test was used to examine the impact of CysC on survival. Univariate and multivariate risk factor analyses were performed using Cox regression. Multivariate analysis included all values with $P < .05$. Continuous variables are presented as median (range), if not otherwise specified. Categorical variables are presented as absolute cases or percentage. All data were analysed using SPSS (version 24, IBM, Armonk, NY, USA) and plotted using Prism (version 6, GraphPad, LaJolla, CA, USA). A $P< 0.05$ was considered statistically significant.

TABLE 1 General characteristics of the patients included in this study (N = 173)

	All patients
Number of patients	173
Age (years)	59 (18-83)
Gender (male/female)	105/68
MELD score	11(6-30)
Child-Pugh score (A/B/C)	32/118/23
Etiology of cirrhosis (alcoholic/hepatitis/other)	127/20/25
Indication for TIPS (bleeding/ascites/both)	63/93/17
Oesophageal varices (no/small/large)	27/115/31
Hepatorenal syndrome (absent/HRS1/HRS2)	129/24/17
Serum creatinine (mg/dL)	1.1(0.48-8.2)
Beta-trace protein (mg/L)	0.85 (0.33-6.64)
Cystatin C (mg/L)	1.2 (0.44-6.46)
Median follow-up (days)	336 (103-608)

Note: Data are presented as mean (standard deviation) or median (interquartile range) and frequency (percentage).
Abbreviations: MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.

3 | RESULTS

3.1 | General characteristics of the patients and their association with CysC and BTP

The patients included in this study were mainly male (60%) with a median age of 59 (18-83) years. Median MELD score was 11 (6-30) and most were Child-Pugh B patients (68%). Overall, 32 patients were Child-Pugh A, 118 patients Child-Pugh B and 23 patients Child-Pugh C (Table 1). Etiology of cirrhosis was mainly alcoholic (74%), and the main indication was resistant or refractory ascites (64%).

The levels of creatinine, CysC and BTP were similar in both cohorts prior to TIPS insertion. Both, CysC and BTP showed a strong

TABLE 2 Correlations of cystatin C and beta-trace protein with baseline liver and baseline/follow-up kidney function parameters in patients with cirrhosis receiving TIPS

	Cystatin C		Beta-trace protein	
	Rs	*P*-value	Rs	*P*-value
Child-Pugh score	0.3	<.001	0.22	.005
MELD score	0.59	<.001	0.52	<.001
Serum creatinine				
Baseline (at TIPS)	0.72	<.001	0.68	<.001
1 month after TIPS	0.78	<.001	0.78	<.001
2 months after TIPS	0.78	<.001		
Blood urea nitrogen (BUN)				
Baseline (at TIPS)	0.55	<.001	0.44	<.001
1 month after TIPS	0.44	<.001	0.36	.004

Note: Non-parametric correlation (spearman) analysis showing the association of cystatin C and BTP levels with hepatic function scores (Child-Pugh score, MELD score) and renal function parameters (serum creatinine and BUN levels). Renal function parameters were recorded at baseline and at follow-up.
Abbreviations: MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt; Rs, Spearman coefficient.

correlation with each other (Rs 0.87, $P < .01$). CysC and BTP correlated significantly with the MELD and Child-Pugh scores at TIPS implantation. Moreover, CysC and BTP showed strong correlations with kidney parameters, such as creatinine, blood urea nitrogen and urinary sodium excretion at TIPS and during short-term follow-up (Table 2). Also, CysC and BTP levels increased in parallel with Child-Pugh score (Table 2).

3.2 | Prognostic value of CysC and BTP in the whole cohort

Univariate regression time-to-event analysis indicated that several variables were significantly associated with mortality (Table S1). Besides MELD, Child-Pugh score, bilirubin and creatinine, CysC and BTP were also identified as factors significantly associated with overall mortality. When these factors were analysed using Cox regression multivariate time-to-event analysis, CysC was the only independent factor associated with overall survival (HR = 1.66, 95%-CI 1.34-2.06, Table S1). Of note, there was no effect of TIPS indication (refractory ascites or recurrent bleeding). AUROC analysis revealed CysC levels of 1.55 mg/L as the best cut-off to predict overall survival (Figure 1A), which was confirmed in the Kaplan-Meier plot (Figure 1B).

3.3 | Sex effect of cystatin C and BTP

Interestingly, CysC levels were lower in female patients than in male patients. In order to elaborate this finding further, the general

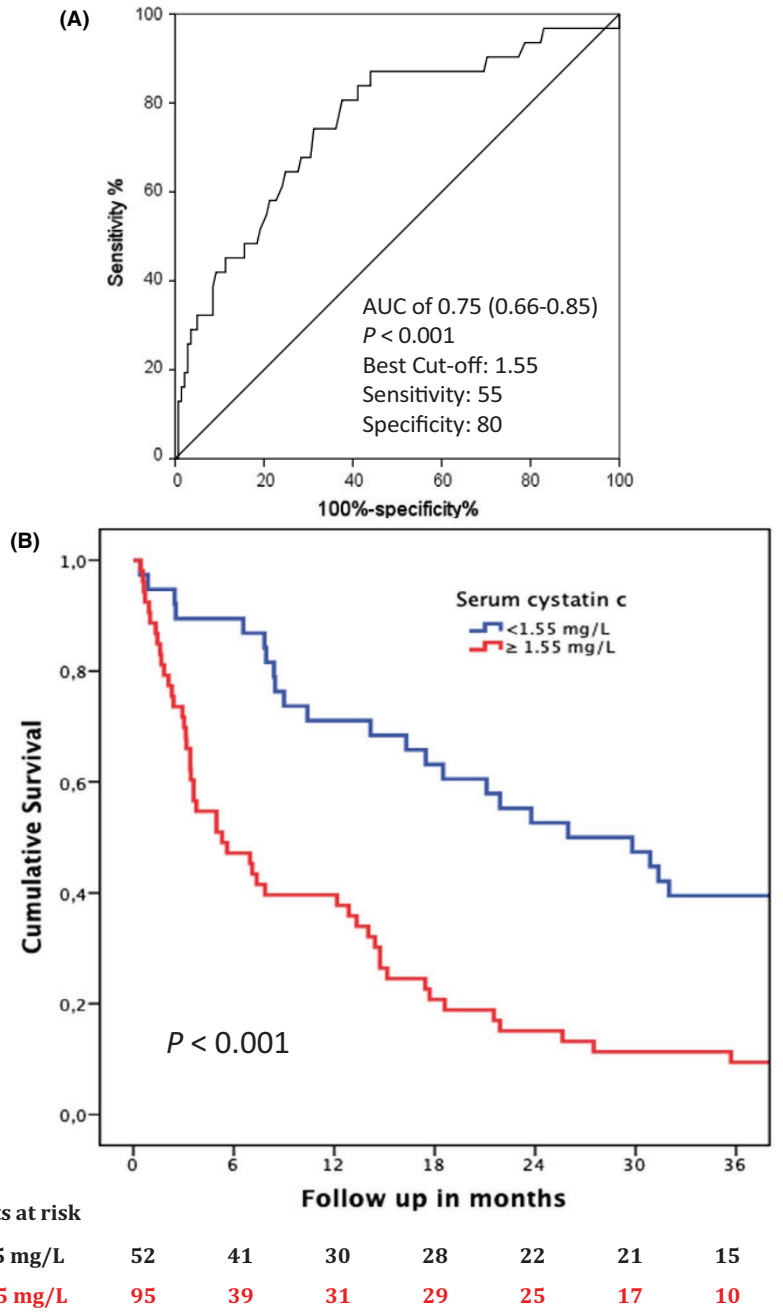

FIGURE 1 Depicts CysC AUROC in order to identify the cut-off in the total cohort. AUC of 0.75 identified CysC levels of 1.55 mg/L as the best cut-off for predicting mortality in the total cohort (A) and confirmed by the Kaplan-Meier plot with log-rank test (B)

characteristics of male patients were compared to those of the female patients (Table 3). Male patients showed a significantly higher proportion of alcoholic cirrhosis (79% vs 66%), higher levels of MELD scores, creatinine and higher rate of HRS (Table 3).

In order to account for this imbalance at baseline between males and females a (1:1) propensity score matching of the entire cohort for males and females was performed adjusted for age, MELD, etiology and TIPS indication. Sixty-four males and 64 females were included for further analysis (Table 3).

Owing to these significant differences in the severity of liver disease, uni- and multivariate time-to-event analysis were used to assess the variables associated with survival in male and female patients. While in the univariate time-to-event analysis the results were similar between both groups (Table 4) and also to the results presented in the whole cohort (Table S1), multivariate analysis revealed surprising results (Table 4). While in male patients, creatinine (HR = 1.54, 95%-CI 1.25-1.89) was the only factor independently associated with overall survival, in female patients, only CysC (HR = 3.16, 95%-CI 1.36-7.35) was independently associated with overall survival (Table 4).

AUROC analysis revealed 1.62 mg/L as the best CysC cut-off for male and 1.47 mg/L for female patients, (Figure 2A,2). Kaplan-Meier plots confirmed these results (Figure 2C,2).

4 | DISCUSSION

This study shows that cystatin C is also able to predict longer term survival in patients receiving TIPS, thereby confirming previous data and extending their value to the TIPS population. More importantly, our work demonstrates that the renal dysfunction markers show sex specificity in terms of prognostic values. This opens for discussion the role of sex-specific assessment of kidney dysfunction in cirrhosis.

Cystatin C has long been described as a suitable marker to assess kidney function in cirrhosis.[15] In this study, we could confirm that in patients with severe portal hypertension and kidney dysfunction, CysC is also a suitable marker of kidney function. In addition, beta-trace protein presented a very strong correlation with creatinine in the follow-up of the study patients. The sequential measurement of creatinine and follow-up of the patients is another strength of this study, demonstrating that cystatin C and beta-trace protein have predictive values for the development of kidney function in patients with cirrhosis receiving TIPS. Importantly, the correlation of CysC and beta-trace protein with Child-Pugh score – while still significant – showed weak correlation at least at baseline, suggesting that CysC and beta-trace protein were correlated with the potential of recovery of kidney function after TIPS in these patients rather than the actual status at the time when these levels are determined. This prognostic value of CysC, in particular, and to a lesser extent also of beta-trace protein, has not been demonstrated previously, since previous research focused more on the estimation of kidney function at the time of determination.[15]

By contrast, cystatin C has gained attention in recent years not only as a renal dysfunction biomarker in different diseases,[16-18] but also in patients with initial stages of liver disease, where it has been used to assess kidney dysfunction.[19] Recently, cystatin C was shown to estimate kidney dysfunction better than creatinine.[11] The authors investigated a large cohort of more than 700 patients and were also able to identify a certain sex specificity in the estimation of kidney function.[11] Our study further elaborates these findings

TABLE 3 General characteristics of the whole cohort stratified by sex

	Male	Female	*P*-value	Male	Female	*P*-value
Number of patients	105	68		64	64	
Age	59 (18-83)	58 (29-80)	.68	58 (18-80)	58 (30-80)	.315
MELD score	11 (6-30)	10 (6-25)	**.02**	11 (6-28)	10 (6-25)	.173
Child-Pugh score (A/B/C)	16/72/17	16/46/6	.08	11/42/11	15/44/5	.233
Etiology of cirrhosis (alcoholic/hepatitis/other)	83/11/11	46/9/14	**.04**	42/11/11	44/9/11	.884
Indication for TIPS (bleeding/ascites/both)	38/57/10	26/36/6	.78	23/40/1	24/34/6	.130
Serum creatinine (mg/dL)	1.2 (0.67-8.2)	0.9 (0.48-5.7)	**<.001**	1.2 (0.67-8.2)	0.9 (0.48-5.7)	**<.001**
Beta-trace protein (mg/L)	0.9 (0.33-6.64)	0.81 (0.42-1.99)	.15	0.9 (0.38-6.64)	0.81 (0.42-1.89)	.15
Cystatin C (mg/d)	1.3 (0.44-6.46)	1.17 (0.53-2.6)	**.048**	1.3 (0.59-6.46)	1.16 (0.53-2.6)	**.033**
Hepatorenal syndrome (absent/HRS1/HRS2)	73/18/13	56/6/4	**.03**	45/11/8	53/6/4	.178
Oesophageal varices (no/small/large)	15/67/23	12/48/8	.13	13/35/16	11/45/8	.130

Note: Data presented as mean (standard deviation) or median (interquartile range) and frequency (percentage) and tested using non-parametric Mann-Whitney-U-test. Bold value indicates significance of *P*-values.
Abbreviations: MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.

TABLE 4 Survival predictors stratified by sex. Univariate and multivariate Cox-regression analysis

	Univariate analysis			Multivariate analysis		
Variables	***P*-value**	**Hazard ratio**	**Variables**	***P*-value**	**Hazard ratio**	**Variables**
Males (n = 92)						
Cystatin C	0.001	1.51	1.19-1.91			
Beta-trace protein	0.004	1.29	1.09-1.52			
Child-Pugh score	0.036	1.26	1.02-1.55			
MELD score	<0.001	1.1	1-05-1.16			
Bilirubin	0.003	1.31	1.1-1.55			
Creatinine	<0.001	1.51	1.24-1.85	<0.001	1.54	1.25-1.89
Females (n = 55)						
Cystatin C	0.006	3.32	1.42-7.75	0.009	3.17	1.34-7.52
Beta-trace protein	0.024	2.97	1.15-7.63			

Abbreviations: MELD, model for end-stage liver disease

and confirms previous data, namely that CysC is a good predictor of kidney dysfunction and, as outlined above, it estimated the development of renal function after TIPS. However, we could not observe an independent predictive value in our collective. Therefore, CysC demonstrated good predictive abilities for overall survival in patients with liver disease, independent of sex. This finding is also in line with the findings from the CANONIC study.[20] Patients admitted with acute decompensation of cirrhosis and are at risk of developing

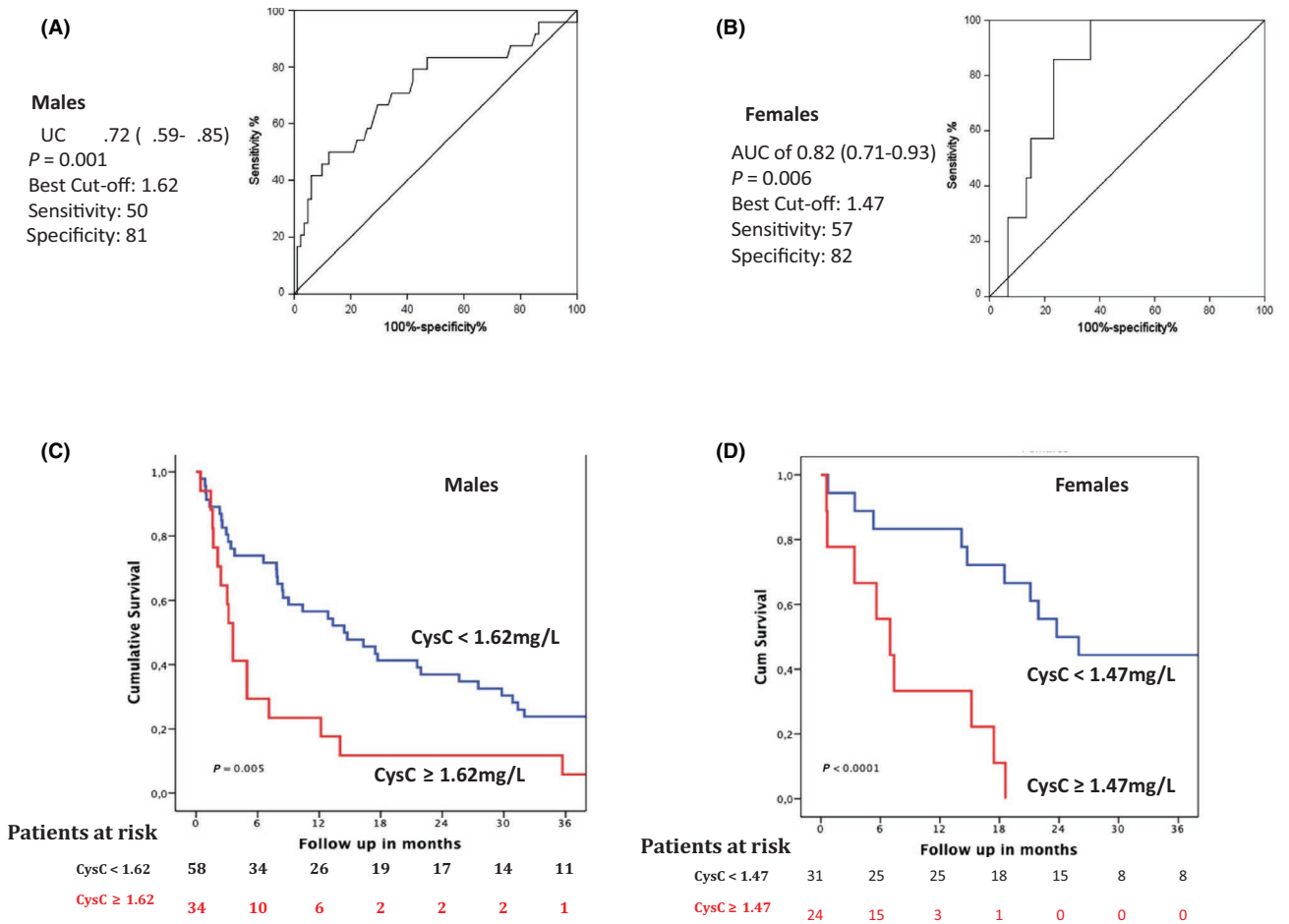

FIGURE 2 Depicts CysC stratified by sex. AUROC of CysC revealed in male patients (n = 92), an AUC of 0.72 in males with the best cut-off of 1.62 mg/L (A) and in female patients (n = 55), an AUC of 0.82 with a cut-off of 1.47 mg/L (B). C, D, Show the Kaplan-Meier curves using the sex-specific cut-offs for male (C) and female patients (D)

acute kidney injury and acute-on-chronic liver failure, as well as fatal outcome, can be identified by CysC levels.[12] Interestingly, we identified identical cut-off levels in our cohort of patients receiving TIPS in this study, although without relationship to a specific cause of death. This is noteworthy since our two cohorts were recruited at different time points and received different standard therapies according to guidelines. Another recent and large study also described that cystatin C could predict the development of AKI and that its combination with MELD or Child-Pugh scores could predict survival more accurately.[13] The authors obtained their results from a cohort of 531 patients including a derivative cohort of 273 patients and a validation cohort of 258 patients. This fact may be interpreted as external validation of our data and underlines the robustness and reproducibility of our findings.[13]

Recent advances in the understanding of cystatin C levels in the prediction of sex-specific outcome greatly contributed to our results.[10,11] It is now apparent as to why in female patients, CysC and not creatinine provides the best estimate of survival, since it seems not to be dependent on muscle mass, but rather on subcutaneous fat.[21] By contrast, in male patients, sarcopenia plays an important role.[10,11,22] This phenomenon explains why the cut-off for sarcopenia needs to be sex-specific, similarly to the prognostic value of the turnover of basal membrane proteins such as collagen type IV, as shown recently.[23,24] All this evidence explains why in our study, when analysed separately in male patients, creatinine, which is strongly linked to muscle mass, is the best predictor of mortality, whereas in female patients, it is CysC. Our data are parallel to reports highlighting the fact that female patients are at a disadvantage in the liver transplantation waiting list.[25] Our findings could serve as a basis for reassessment of new models that include these sex-specific parameters, thus improving the allocation of transplants, which are currently MELD-based and thereby favouring male recipients.[25]

Our study has several limitations, starting at the retrospective design of analysis, although data and samples were collected prospectively. Also, there is no comparison of kidney function apart from creatinine and BUN levels. Finally, the cohort, while very well characterized, is not as large as that of the previously published reports. However, our data and measurements are well in line with previous reports, regarding determination of the cut-offs and their prognostic value, thus underlining their robustness.

In conclusion, our study provides further evidence for consideration of new sex-related parameters, such as cystatin C for therapeutic purposes (ie hepatic transplant allocation) in order to design a 'tailored score' since current allocation procedures possibly overestimate transplant-free survival in female patients at least after TIPS-placement.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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