Low Serum Cholinesterase Identifies Patients With Worse Outcome and Increased Mortality After TIPS

Lena Stockhoff ,[1] Theresa Muellner-Bucsics ,[2,3] Antoaneta A. Markova,[4] Marie Schultalbers,[1] Simone A. Keimburg,[4] Tammo L. Tergast,[1] Jan B. Hinrichs,[5] Nicolas Simon,[6] Svetlana Gerbel,[6] Michael P. Manns,[1] Mattias Mandorfer ,[2,3] Markus Cornberg,[1] Bernhard C. Meyer,[5] Heiner Wedemeyer,[1,4] Thomas Reiberger ,[2,3] and Benjamin Maasoumy[1]

Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for portal hypertension-related complications. However, careful selection of patients is crucial. The aim of this study was to evaluate the prognostic value of serum cholinesterase (CHE) for outcomes and mortality after TIPS insertion. In this multicenter study, 389 consecutive patients with cirrhosis receiving a TIPS at Hannover Medical School, University Hospital Essen, or Medical University of Vienna were included. The Hannover cohort (n = 200) was used to initially explore the role of CHE, whereas patients from Essen and Vienna served as a validation cohort (n = 189). Median age of the patients was 58 years and median Model for End-Stage Liver Disease (MELD) score was 12. Multivariable analysis identified MELD score (hazard ratio [HR]: 1.16; $P < 0.001$) and CHE (HR: 0.61; $P = 0.008$) as independent predictors for 1-year survival. Using the Youden Index, a CHE of 2.5 kU/L was identified as optimal threshold to predict post-TIPS survival in the Hannover cohort ($P < 0.001$), which was confirmed in the validation cohort ($P = 0.010$). CHE < 2.5 kU/L was significantly associated with development of acute-on-chronic liver failure ($P < 0.001$) and hepatic encephalopathy ($P = 0.006$). Of note, CHE was also significantly linked to mortality in the subgroup of patients with refractory ascites ($P = 0.001$) as well as in patients with high MELD scores ($P = 0.012$) and with high-risk FIPS scores ($P = 0.004$). After propensity score matching, mortality was similar in patients with ascites and CHE < 2.5 kU/L if treated by TIPS or by paracentesis. Contrarily, in patients with CHE ≥ 2.5 kU/L survival was significantly improved by TIPS as compared to treatment with paracentesis ($P < 0.001$). *Conclusion:* CHE is significantly associated with mortality and complications after TIPS insertion. Therefore, we suggest that CHE should be evaluated as an additional parameter for selecting patients for TIPS implantation. (*Hepatology Communications* 2021;0:1-12).

An effective and established treatment option for patients with decompensated liver cirrhosis is the insertion of a transjugular intrahepatic portosystemic shunt (TIPS).[1] TIPS placement reduces the need for large volume paracentesis and decreases bleeding-related mortality and the risk for further variceal bleedings.[1,2] In patients with refractory ascites (RA), overall survival was superior compared with repetitive paracentesis in some studies.[3,4] However, proper selection of patients eligible for TIPS

Abbreviations: ACLF, acute-on-chronic liver failure; CHE, cholinesterase; EASL, European Association for the Study of the Liver; FIPS, Freiburg index of post-TIPS survival; GGT, gamma-glutamyl transferase; HE, hepatic encephalopathy; HR, hazard ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; MHH, Hannover Medical School; PSG, portosystemic pressure gradient; RA, refractory ascites; ROC, receiver operating characteristic; sHR, subdistribution HR; TIPS, transjugular intrahepatic portosystemic shunt.

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is crucial, as the direct shunting of portal venous blood can even be harmful in certain patients, including those with very advanced stages of liver disease.[5,6] Of note, definite selection criteria for TIPS insertion are not indisputably established to date. Most suggested criteria are based on TIPS studies either lacking a non-TIPS control group or lacking an external validation cohort.[7,8] According to the latest guidelines released by the European Association for the Study of the Liver (EASL), TIPS is not recommended in patients suffering from recurrent or overt hepatic encephalopathy (HE), heart failure, active infection, bilirubin >3 mg/dL and a platelet count <75,000/μL, progressive kidney failure, or pulmonary hypertension.[1] Of note, none of the suggested parameters is suitable to reflect hepatic synthetic capacity.

Serum cholinesterase (CHE) is an acetylcholine hydrolyzing enzyme and is almost entirely synthesized in hepatocytes.[9] Therefore, low CHE levels are often used as a surrogate marker for impaired hepatic synthetic capacity.[10] In contrast to albumin, it is not influenced by intravenous supplementations in clinical practice. CHE activity is used in hepatobiliary surgery to predict outcome after liver resection and/or other treatment of liver cancer in some countries[11] and has been suggested as a prognostic marker for those undergoing liver transplantation.[12] Most recently it has been demonstrated that CHE activity is also closely associated with sarcopenia and the nutritional status.[13,14] Both hepatic function as well as sarcopenia have been linked to complications after TIPS insertion.[15-17] Thus, we hypothesize that CHE activity may help to predict post-TIPS outcome. Of note, the prognostic value of CHE activity in the context of TIPS placement has not been evaluated so far. Currently, many medical centers do not include CHE in their routine laboratory panels, leaving the potential value of CHE activity as a predictive marker unconsidered.

The aim of this study was to investigate the prognostic capability of serum CHE activity as a predictor for mortality and complications after TIPS insertion.

Materials and Methods

TIPS COHORTS

All consecutive patients with liver cirrhosis receiving a TIPS at Hannover Medical School (MHH) (Hannover, Germany) between January 2012 and December 2018 (n = 232) were automatically identified by the Enterprise Clinical Research Data Warehouse using the respective German operation and procedure code (Supporting Fig. S1).[18,19] Subsequently, all patients without a clinical diagnosis of liver cirrhosis (n = 7), with Budd Chiari syndrome (n = 20), and without sufficient informed consent (n = 4) were excluded. Overall, 201 TIPS patients were eligible, of whom 1 patient was excluded because of missing baseline laboratory values. All patients receiving a TIPS

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ARTICLE INFORMATION:

From the [1]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [2]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [3]Vienna Hepatic Hemodynamic Laboratory, Medical University of Vienna, Vienna, Austria; [4]Department of Gastroenterology and Hepatology, University Hospital Essen, Essen, Germany; [5]Institute for Diagnostic and Interventional Radiology, Hannover Medical School, Hannover, Germany; [6]Center for Information Management (ZIMt), Hannover Medical School, Hannover, Germany.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Benjamin Maasoumy, PD Dr. med.
Department of Gastroenterology
Hepatology and Endocrinology, Hannover Medical School
Carl-Neuberg-Str.1
30625 Hannover, Germany
E-mail: maasoumy.benjamin@mh-hannover.de
Tel.: 0049-5115326529

for secondary prophylaxis of variceal bleeding underwent an elective TIPS procedure. Patients receiving a TIPS under urgent conditions due to uncontrolled bleeding or as "early TIPS" within 72 hours after variceal bleeding were excluded from the current analysis. For external validation, an almost equally sized validation cohort of 189 TIPS patients from the Medical University of Vienna (Vienna, Austria; n = 144; 2000-2017)[20] and University Hospital Essen (Essen, Germany; n = 45; 2016-2019) was used.

PARACENTESIS COHORT

To compare treatment with TIPS versus paracentesis in patients with RA, a propensity score matching was performed. Patients eligible for the paracentesis control group were recruited from the well-defined Hannover Ascites Cohort.[21,22] Albumin substitution was used after large-volume paracentesis.[1] Overall, 527 patients without TIPS placement were eligible and carefully checked manually for the inclusion and exclusion criteria for the current study: 37 patients were excluded, as they did not fulfil all criteria of refractory/recurrent ascites; 63 patients were excluded due to acute clinical deterioration at index paracentesis, and 4 patients due to Budd Chiari syndrome (Supporting Fig. S2). To minimize selection bias, patients fulfilling any TIPS contraindication in concordance with EASL guidelines were excluded (n = 139; chronic HE or HE ≥ grade 2 [n = 94], severe heart failure [n = 26], pulmonary hypertension [n = 10], and hepatocellular carcinoma [n = 9]).[1] Subsequently, 284 patients with cirrhosis and ascites were eligible for matching.

DATA ASSESSMENT

The clinical, laboratory, and TIPS procedure–related data were obtained from patients' medical records. The diagnosis of liver cirrhosis was based on noninvasive methods (i.e., liver ultrasound, elastography, biochemical results, and/or liver biopsy.[23] Baseline was set at the day of TIPS placement (TIPS cohorts) or the first paracentesis at MHH (paracentesis cohort), respectively. Refractory/recurrent ascites was defined as resistant/intractable to diuretic treatment (RA) and/or ascites recurrence of 3 times or more within 1 year (recurrent ascites).[24] HE was classified according to West Haven criteria,[4] and acute-on-chronic liver failure (ACLF) was defined based on the EASL–Chronic Liver Failure criteria.[1,25] Terlipressin for treatment of hepatorenal syndrome in the absence of hypotension was not considered as circulatory failure.

TIPS PLACEMENT

TIPS insertion was performed by clinically experienced interventional radiologists according to institutional standard operating procedures.[26,27] TIPS placement was conducted in general anesthesia, and the patients' vital parameters were continuously monitored during the procedure. Covered stent grafts (Viatorr; Gore, Flagstaff, AZ) were used in all patients (Hannover cohort as well as validation cohort). Prosthesis diameter was 8 mm (n = 188) or 10 mm (n = 12) in the Hannover cohort and 7 mm (n = 1), 8 mm (n = 49), 10 mm (n = 126), or 12 mm (n = 2) in the validation cohort (stent diameter was not available in 11 patients). After successful TIPS placement, all patients were monitored at an intensive care unit for 24 hours. Before discharge as well as in every outpatient follow-up visit, TIPS patency was confirmed, and TIPS flow was measured by ultrasound conducted by an experienced physician.

STUDY DESIGN

Primary endpoint was 1-year mortality after TIPS placement. Patients were censored if they underwent liver transplantation or at the end of follow-up. Secondary endpoints were development of ACLF and HE at 28 days and 90 days after TIPS insertion. Death and liver transplantation were considered as competing events.

To compare treatment with TIPS versus paracentesis in patients suffering from refractory/recurrent ascites, a 1:1 propensity score matching was used.[28-30] In the first approach, all patients with a CHE < 2.5 kU/L (n = 197 paracentesis patients and n = 91 TIPS patients) and in the second approach all patients with a CHE ≥ 2.5 kU/L were included (n = 87 paracentesis patients and n = 68 TIPS patients). Only patients receiving a TIPS for RA were considered for the matching.

STATISTICS

All statistical analyses were performed using SPSS (IBM SPSS Statistics, Versions 25 and 26), R Version

3.3.3 (with R packages "cmprsk,"[31,32] "crrstep,"[31,33] "MatchIt,"[34] "RItools,"[35] and "cem"[36]). Continuous variables are presented as median with interquartile range (IQR) and were compared using the Mann-Whitney U test for unpaired data or the Wilcoxon signed-rank test for paired data. Categorical variables are shown as numbers with percentages and were compared using a chi-squared test or Fisher's exact test, as appropriate. McNemar test was used for comparison of paired categorical variables. For selection of an optimal CHE cut-off, receiver operating characteristic (ROC) analysis with 1-year mortality as endpoint was performed. The CHE cut-off, for which the Youden Index was maximal, was selected for further analysis. Survival was analyzed using the log-rank test. To adjust for potential confounders, univariable and multivariable Cox regression analysis (backward stepwise regression) was conducted including the following parameters: age, pre-TIPS portosystemic pressure gradient (PSG), albumin, MELD score, TIPS indication (RA vs. bleeding), and serum CHE activity. ACLF and HE were investigated using a competing risk analysis, treating death and liver transplantation as competing events. After estimation of the respective cumulative incidence function from competing risk data, estimates were compared using a modified chi-squared test.[31,32] To identify predictors for the occurrence of ACLF and HE, a backward multivariable competing risk regression model was implemented, in which the parameters age, PSG before and after TIPS insertion, MELD, HE before TIPS, TIPS indication, and CHE activity were included.[31,33] In all analyses, $P < 0.05$ was considered as statistically significant.

Propensity score matching was performed using a 1:1 nearest neighbor matching procedure based on the greedy matching algorithm.[37] Matching covariates were MELD score, age, sex, platelet count, sodium, and CHE activity. A caliper of width equal to 0.2 of the SD of the logit of the propensity score was used for the matching procedure. The standardized mean differences (SMDs) of the matching covariates were calculated to validate model adequacy. Subsequently, a stratified log-rank test was used to analyze the survival of patients treated with either TIPS or paracentesis, respectively.

ETHICS

The retrospective analysis was approved by the local ethics committee of the participating centers (votes: Hannover: 7935_BO_K_2018; Vienna: EK 1760/2014; Essen: Nu20-9192-BO) and followed the principles outlined in the Declaration of Helsinki.

Results

BASELINE CHARACTERISTICS OF TIPS PATIENTS IN THE HANNOVER COHORT

Overall, 200 TIPS patients from MHH were included in this study with a median MELD of 12, median CHE activity of 2.48 kU/L (normal range: 5.32-12.92 kU/L), and a median age of 58 years. Fifty-six percent of the patients were males. The median pre-interventional PSG was 16.2 mmHg and median postinterventional PSG was 5.9 mmHg, resulting in a median PSG reduction of 65%. Most of the patients (76%) received TIPS placement for RA. The most-frequent etiology of cirrhosis was alcohol-associated liver disease (58%) (Table 1).

PROGNOSTIC VALUE OF CHE ACTIVITY FOR SURVIVAL AFTER TIPS INSERTION

Using univariate Cox regression analysis, CHE activity was highly associated with 1-year survival in the Hannover cohort (per kU/L; HR: 0.51; $P < 0.001$). When adjusting for age, PSG, MELD score, albumin, and TIPS indication (RA vs. bleeding), CHE activity remained an independent predictor for 1-year mortality after TIPS placement (HR: 0.61; $P = 0.008$; Table 2). Of note, MELD score was also highly associated with 1-year survival (HR: 1.16; $P < 0.001$), whereas the other parameters were not independently predictive. When considering the single parameters for calculating the MELD score separately, CHE activity as well as creatinine levels were identified as independent predictors for 1-year survival (Supporting Table S1).

To determine the optimal CHE cut-off for predicting 1-year mortality, a ROC analysis was performed, resulting in an area under the curve of 0.721 (Supporting Fig. S3). Youden Index was maximal when selecting a CHE cut-off of 2.5 kU/L. Survival 1 year after TIPS placement of patients with CHE activity < 2.5 kU/L was significantly lower compared

TABLE 1. BASELINE CHARACTERISTICS OF TIPS PATIENTS OF MHH IN DEPENDENCE OF BASELINE CHE ACTIVITY

	All Patients	CHE ≥ 2.5 kU/L	CHE < 2.5 kU/L	*P* Value
Patients (n, %)	200 (100)	97 (49)	103 (51)	
Age (years)	58 (51-67)	59 (51-67)	57 (51-67)	0.766
Male/female (n, %)	113 (56)/87 (44)	51 (53)/46 (47)	62 (60)/41 (40)	0.278
TIPS indication*				
Refractory ascites (n, %)	151 (76)	64 (66)	87 (84)	0.003
Bleeding (n, %)	49 (25)	33 (34)	16 (16)	0.003
Hepatic hydrothorax (n, %)	7 (3)	2 (2)	5 (5)	0.445
Etiology of cirrhosis*				
Viral (n, %)	24 (12)	4 (4)	20 (19)	0.001
Alcohol (n, %)	116 (58)	57 (59)	59 (57)	0.740
NASH (n, %)	16 (8)	9 (9)	7 (7)	0.545
Other (n, %)	49 (25)	28 (29)	21 (20)	0.189
MELD	12.0 (10.0-15.0)	11.0 (9.0-14.0)	13.0 (11.0-16.0)	<0.001
Child Pugh				
Class A (n, %)	11 (6)	10 (10)	1 (1)	0.004
Class B (n, %)	170 (85)	83 (86)	87 (84)	0.782
Class C (n, %)	19 (9)	4 (4)	15 (15)	0.014
PSG before TIPS (mmHg)	16.2 (13.2-19.5)	16.0 (13.2-19.1)	16.2 (13.6-19.9)	0.279
PSG after TIPS (mmHg)	5.9 (4.0-7.4)	5.1 (4.0-7.2)	5.9 (4.0-7.4)	0.240
% reduction of PSG	65.0 (55.4-73.3)	65.1 (57.6-74.7)	65.0 (53.8-72.3)	0.475
CHE (kU/L)	2.48 (1.81-3.47)	3.54 (2.89-4.34)	1.82 (1.30-2.17)	<0.001
Bilirubin (μmol/L)	17 (11-26)	15 (10-21)	20 (12-30)	0.002
Creatinine (μmol/L)	98 (73-134)	87 (68-123)	104 (77-142)	0.046
INR	1.28 (1.17-1.41)	1.22 (1.14-1.34)	1.36 (1.23-1.48)	<0.001
Sodium (mmol/L)	136 (132-139)	136 (134-139)	135 (131-138)	0.065
Platelets (10^3/μL)	116 (77-174)	120 (78-171)	110 (77-179)	0.397
Albumin (g/L)	28 (24-32)	30 (27-34)	27 (24-30)	<0.001
AST (U/L)	44 (33-57)	45 (33-56)	43 (33-61)	0.819
ALT (U/L)	24 (17-38)	26 (18-40)	22 (14-34)	0.033
ALP (U/L)	131 (91-180)	135 (97-188)	119 (89-174)	0.124
GGT (U/L)	124 (68-231)	131 (75-253)	109 (58-184)	0.132

Note: Mann-Whitney U test was used for continuous variables, chi-squared test, or Fisher's exact test for categorical variables. Data are presented as median with IQR or numbers with percentages.
*Some patients have mixed TIPS indication and/or mixed etiology of cirrhosis. Therefore, the summation of percentages results in >100% in these columns.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; NASH, nonalcoholic steatohepatitis.

to those with a CHE ≥ 2.5 kU/L ($P < 0.001$; sensitivity 85.3%, specificity 56.0%, negative predictive value 94.8%, and positive predictive value 28.4%) (Fig. 1A). Importantly, this finding was confirmed in the external multicenter validation cohort ($P = 0.010$; Fig. 1B and Supporting Table S2 for baseline characteristics). Moreover, CHE activity was found to be significantly higher 1 year after TIPS insertion as compared with baseline (Supporting Fig. S4). We further stratified the value of CHE depending on the MELD score. A MELD threshold of 15 was identified as optimal cut-off to predict mortality after TIPS insertion in our cohort using ROC analysis and the Youden Index method. Of note, CHE activity was still significantly associated with mortality in the subgroups of patients with a MELD score ≤ 15 ($P = 0.005$; Fig. 2A) as well as with a MELD score > 15 ($P = 0.012$; Fig. 2B). Furthermore, we tested the prognostic value of CHE activity in the subgroups of patients with high-risk and low-risk Freiburg index of post-TIPS

TABLE 2. UNI- AND MULTIVARIABLE COX REGRESSION ANALYZING RISK FACTORS FOR 1-YEAR SURVIVAL AFTER TIPS PLACEMENT IN THE HANNOVER COHORT

	Univariate			Multivariable		
Risk Factor	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)	1.033	1.002-1.066	0.039			
PSG before TIPS (mmHg)	1.046	0.981-1.115	0.168			
MELD	1.187	1.111-1.268	<0.001	1.161	1.080-1.247	<0.001
CHE (kU/L)	0.507	0.353-0.728	<0.001	0.607	0.420-0.875	0.008
Albumin (g/L)	0.960	0.904-1.020	0.186			
TIPS indication refractory ascites	1.885	0.731-4.858	0.190			

Note: All parameters tested in the univariate analysis were included in the multivariable model.

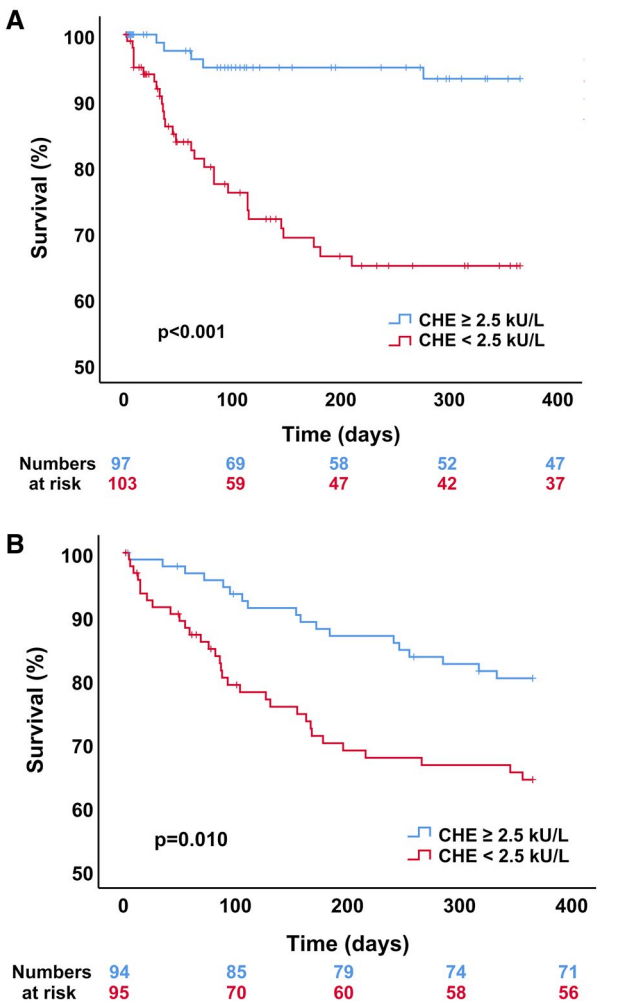

FIG. 1. Survival of TIPS patients in dependence of CHE activity (≥2.5 kU/L vs. <2.5 kU/L). Survival of TIPS patients from the study cohort (MHH) (A) and the external validation cohort (Vienna and Essen) (B) 1 year after TIPS insertion. *P* values were obtained using the log-rank test.

survival (FIPS) scores using our established cut-off of 0.64.[38,39] Interestingly, CHE was significantly linked to survival in low-risk patients (FIPS < 0.64; $P = 0.005$; Fig. 2C) as well as in high-risk patients (FIPS ≥ 0.64; $P = 0.004$; Fig. 2D).

IMPACT OF CHE < 2.5 KU/L ON COMPLICATIONS AFTER TIPS INSERTION

In addition to survival, we also analyzed the effect of low baseline CHE activity on development of ACLF and HE after TIPS insertion in the Hannover study cohort using a competing risk approach. Forty-six patients (23%) developed ACLF within 90 days after TIPS placement. Within this group, 28 patients (61%) suffered from ACLF grade 1, 12 patients (26%) from ACLF grade 2, and 6 patients (13%) from ACLF grade 3. The distribution of organ failures underlying the ACLF episodes was as follows: 47% renal failure, 14% circulatory failure, 12% respiratory failure, 10% cerebral failure, 10% coagulation failure, and 7% liver failure. Patients with a CHE < 2.5 kU/L suffered from significantly more ACLF episodes within 90 days after TIPS insertion than patients with CHE > 2.5 kU/L ($P < 0.001$; Fig. 3A). After adjusting for potential confounders, CHE activity was still significantly associated with ACLF development 28 days after TIPS implantation (subdistribution HR [sHR]: 0.60; $P = 0.010$) as well as 90 days after TIPS insertion (sHR: 0.66; $P = 0.011$; Table 3A). As most ACLF episodes occurred early after TIPS insertion, we hypothesize that they might be related to the TIPS procedure itself, which was performed in general anesthesia at our center. The relatively high number of

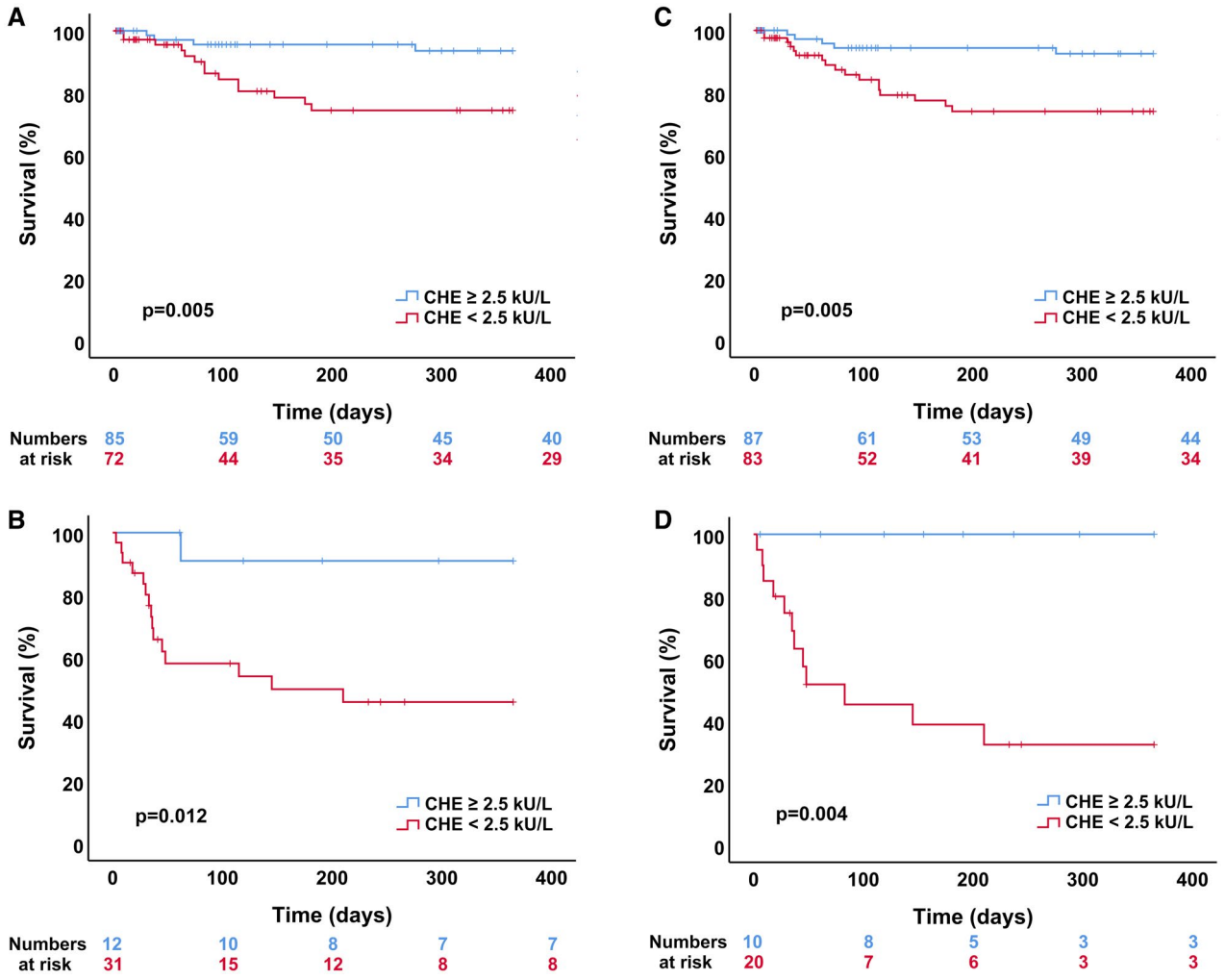

FIG. 2. Survival of TIPS patients in MELD and FIPS subgroups in dependence of CHE activity (≥2.5 kU/L vs. <2.5 kU/L). Survival of TIPS patients with a MELD score ≤ 15 (A) and a MELD score > 15 (B). Survival of TIPS patients with a low-risk FIPS score (<0.64) (C) and a high-risk FIPS score (≥0.64) (D). *P* values were obtained using the log-rank test.

ACLF episodes in our cohort is very well line with other recently published TIPS cohorts as well as in recent studies investigating the risk of ACLF after surgical interventions.[15,40] This underlines the need for a close and careful monitoring of patients with end-stage liver disease after anesthesia and/or invasive procedures. Moreover, 62 patients (31%) developed HE within 90 days after TIPS insertion, of whom 12 patients (19%) had HE grade 1, 30 patients (49%) had HE grade 2, 18 patients (29%) had HE grade 3, and 2 patients (3%) had HE grade 4. CHE activity was significantly associated with HE development within 90 days after TIPS placement ($P = 0.006$; Fig. 3B). After adjustment for potential confounders, CHE activity was still significantly linked to the occurrence of HE within 28 days after TIPS insertion (sHR: 0.68; $P = 0.033$) as well as 90 days after TIPS insertion (sHR: 0.77; $P = 0.037$; Table 3B).

COMPARISON OF SURVIVAL OF PATIENTS WITH RA TREATED WITH EITHER TIPS VERSUS PARACENTESIS

Because it is still a matter of debate whether TIPS insertion in patients with RA results in prolonged survival as compared to treatment with large-volume paracentesis, the subgroup of patients receiving a TIPS

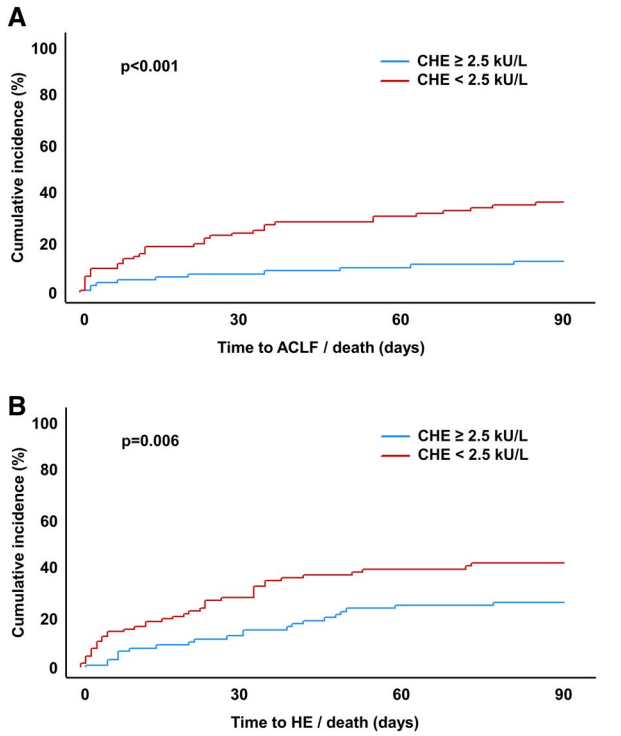

FIG. 3. Occurrence of ACLF and HE in dependence of CHE activity (≥2.5 kU/L vs. <2.5 kU/L). Shown is the cumulative incidence of ACLF (A) and HE (B) 90 days after TIPS insertion in the Hannover cohort in dependence of CHE activity calculated by competing risk analysis. Death and liver transplantation were considered as competing events.

for RA was separately evaluated in an additional analysis. The CHE cut-off 2.5 kU/L predicting 1-year survival after TIPS insertion was confirmed in patients with RA in the Hannover cohort (P = 0.001) as well as in the validation cohort (P = 0.048; Supporting Fig. S5). Moreover, CHE activity remained an independent predictor for 1-year mortality after TIPS insertion in patients with RA in the multivariable model (HR: 0.62; P = 0.019; Supporting Table S3).

We further evaluated the prognostic value of CHE activity in patients undergoing TIPS for RA versus a separate cohort of patients with ascites undergoing treatment with paracentesis. Of note, CHE activity was also significantly associated with survival in patients with recurrent/refractory ascites treated with paracentesis (P = 0.004; Supporting Fig. S6). CHE was still significantly linked to mortality after adjustment for potential confounders (HR: 0.788; P = 0.013; Supporting Table S4).

For adequate comparison of TIPS patients versus paracentesis patients, we performed a 1:1 propensity score matching in the subgroups of patients with baseline CHE < 2.5 kU/L and with baseline CHE ≥ 2.5 kU/L. After matching, an adequate balance was achieved between the groups, which is reflected by small absolute SMDs in the matching covariates (Supporting Table S5). Furthermore, no significant differences between the matched TIPS and paracentesis patients were observed in any of the covariates (Table 4). A subsequent comparison of patients with CHE < 2.5 kU/L managed either with TIPS or paracentesis unveiled no differences in survival at 1 year after baseline (P = 0.857; Fig. 4A). However, when patients with a baseline CHE ≥ 2.5 kU/L were considered, TIPS patients showed a significantly higher 1-year survival compared to patients treated with paracentesis (P < 0.001; Fig. 4B).

Discussion

TIPS insertion is an effective therapy to directly and rapidly decrease portal pressure. According to the most recent high-quality randomized controlled trials as well as many meta-analyses, TIPS placement is, in general, associated with an improved survival as compared with large-volume paracentesis.[1,3,41] However, criteria for optimal patient selection are still a matter of debate. In the present study, we were able to demonstrate that CHE might help to better identify patients who might particularly benefit from TIPS insertion. A low baseline CHE activity was notably associated with poorer survival, which was also confirmed in the equally sized external validation cohort. Of note, CHE activity was still able to separate patients with poorer survival in the subgroups of patients with advanced liver disease (MELD > 15) as well as with a high-risk FIPS score. Furthermore, a low CHE activity was independently linked to a higher incidence of ACLF and HE after TIPS placement. Of note, survival of patients with RA managed with TIPS was similar to that of patients treated with paracentesis when baseline CHE activity was <2.5 kU/L. However, if baseline CHE activity was ≥2.5 kU/L, TIPS patients had a significantly superior survival compared to those treated with paracentesis.

So far, many parameters were suggested for the prediction of post-TIPS outcome. Bureau et al. postulated

TABLE 3A. BACKWARD MULTIVARIABLE COMPETING RISK MODEL FOR ACLF DEVELOPMENT 28 DAYS AND 90 DAYS AFTER TIPS INSERTION IN THE HANNOVER COHORT

	28 Days			90 Days		
Risk Factor for ACLF	sHR	95% CI	*P*	sHR	95% CI	*P*
PSG before TIPS (mmHg)	0.891	0.808-0.982	0.021	0.932	0.867-1.002	0.059
MELD	1.120	1.137-1.266	<0.001	1.174	1.110-1.241	<0.001
CHE (kU/L)	0.604	0.413-0.883	0.010	0.656	0.476-0.905	0.011

Note: Death and liver transplantation were considered as competing event. Included parameters were age, PSG before TIPS, MELD, CHE activity and TIPS indication (RA vs. bleeding).

TABLE 3B. BACKWARD MULTIVARIABLE COMPETING RISK MODEL FOR HE DEVELOPMENT 28 DAYS AND 90 DAYS AFTER TIPS INSERTION IN THE HANNOVER COHORT

	28 Days			90 Days		
Risk Factor for HE	sHR	95% CI	*P*	sHR	95% CI	*P*
MELD	1.074	0.990-1.165	0.087	1.086	1.019-1.158	0.012
CHE (kU/L)	0.678	0.476-0.967	0.033	0.771	0.605-0.983	0.037

Note: Death and liver transplantation were considered as competing event. Included parameters were age, PSG before TIPS, PSG after TIPS, HE before TIPS, MELD, CHE activity, and TIPS indication (RA vs. bleeding).

TABLE 4A. COMPARISON OF BASELINE CHARACTERISTICS BETWEEN MATCHED PATIENTS WITH CHE < 2.5 KU/L TREATED WITH EITHER TIPS OR PARACENTESIS (90 MATCHED PAIRS)

Paired	All Patients	TIPS	Paracentesis	*P* Value
Patients (n, %)	180 (100)	90 (50)	90 (50)	
MELD	14.0 (12.0-16.0)	13.0 (11.0-16.0)	14.0 (12.0-16.0)	0.331
Sex (male/female)	108 (60)/ 72 (40)	54 (60)/36 (40)	54 (60)/36 (40)	1.000
Age (years)	59 (52-67)	59 (51-67)	59 (53-67)	0.371
Platelets (10^3/µL)	107 (77-180)	115 (80-183)	105 (66-179)	0.258
Sodium (mmol/L)	135 (131-138)	135 (131-138)	136 (132-138)	0.511
CHE (kU/L)	1.82 (1.34-2.13)	1.81 (1.30-2.13)	1.85 (1.39-2.14)	0.514

Note: Wilcoxon signed-rank test was used for continuous variables, and McNemar test for categorical variables. Parameters are presented as median with IQR or numbers with percentages.

TABLE 4B. COMPARISON OF BASELINE CHARACTERISTICS BETWEEN MATCHED PATIENTS WITH CHE ≥ 2.5 KU/L TREATED WITH EITHER TIPS OR PARACENTESIS (51 MATCHED PAIRS)

Paired	All Patients	TIPS	Paracentesis	*P* Value
Patients (n, %)	102 (100)	51 (50)	51 (50)	
MELD	12.0 (10.0-16.0)	12.0 (10.0-15.0)	13.0 (10.0-16.0)	0.787
Sex (male/female)	56 (55)/46 (45)	28 (55)/23 (45)	28 (55)/23 (45)	1.000
Age (years)	60 (53-70)	60 (54-69)	61 (52-71)	0.915
Platelets (10^3/µL)	118 (76-172)	123 (99-171)	111 (71-175)	0.800
Sodium (mmol/L)	136 (134-139)	137 (134-139)	136 (134-139)	0.700
CHE (kU/L)	3.01 (2.74-3.86)	3.04 (2.78-3.98)	2.98 (2.72-3.57)	0.263

Note: Wilcoxon signed-rank test was used for continuous variables, and McNemar test for categorical variables. Parameters are presented as median with IQR or numbers with percentages.

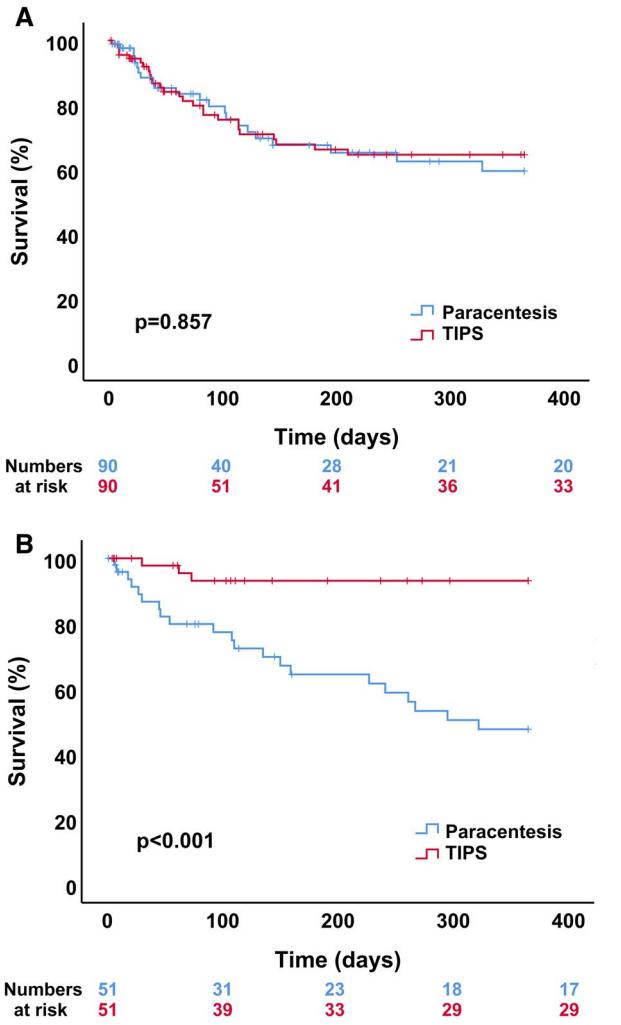

FIG. 4. Comparison of 1-year survival between matched patients with cirrhosis treated with either TIPS or paracentesis. Shown are patients with a baseline CHE < 2.5 kU/L (A) and with a baseline CHE ≥ 2.5 kU/L (B). *P* values were obtained using a stratified log-rank test.

that serum bilirubin as well as platelet count could serve as a selection criterion for TIPS insertion in patients with RA.[7] In accordance with our study, the authors suggested specific cut-offs and elegantly confirmed them in well-defined external validation cohorts, which resulted in broad acceptance of these criteria for TIPS selection. However, no adequate control group consisting of non-TIPS patients was included in that study. A couple of studies demonstrated that a high MELD score is associated with worse outcome after TIPS insertion,[42-45] which was also confirmed in our study. Indeed, the MELD score was originally developed to predict early death after elective TIPS placement.[6] However, the MELD score is not mentioned as a selection criterion for TIPS placement in current guidelines.[1,4] Highly important for post-TIPS outcome might be the hepatic functional capacity, as TIPS may further impair hepatic function by redirecting the portal venous blood flow and advanced liver insufficiency is linked to increased post-TIPS mortality.[46,47] In addition to serum CHE activity, international normalized ratio and albumin are valid markers for hepatic synthetic capacity. However, the patients' serum albumin levels may often fluctuate due to external albumin substitutions (such as in the context of large-volume paracentesis). Another limitation is that albumin measurements are considerably expensive (cost at MHH: 3.40€) compared with other laboratory parameters. We think that serum CHE activity, which can be measured fast and inexpensively (cost at MHH: 0.25€), is an interesting additional parameter when selecting patients for TIPS. However, the potential of CHE activity as an informative routine diagnostic tool might often be underestimated in many clinical centers. Only a few studies specifically investigated the role of CHE in the context of liver diseases, but it is known that a decreased serum CHE activity reflects hepatocellular impairment.[9,10] According to our data, CHE activity is significantly associated with mortality 1 year after TIPS insertion. However, albumin, which is also an indicator of hepatic synthetic capacity, was not predictive for 1-year mortality in our study. Thus, there might be additional factors influencing CHE activity in the patients' serum. Interestingly, an association between low serum CHE activity and sarcopenia was reported in other studies.[13,14] Despite the fact that these findings need to be validated in patients with liver cirrhosis, the link between low CHE levels and sarcopenia in combination with our results would be in accordance with previous findings: Patients, who were sarcopenic at the time of TIPS insertion, had a markedly impaired survival and suffered from more ACLF and HE development after TIPS insertion compared with non-sarcopenic individuals.[15-17]

Patients with severe ascites might often be treated with diuretics first. However, this attempt may take quite some time, while other complications like sarcopenia further progress. Overall, our findings suggest that TIPS insertion might be considered "earlier" in the course of the liver disease, when the patient's hepatic synthetic capacity (and likely the nutritional status) is

still preserved with a serum CHE activity ≥ 2.5 kU/L. In these patients we were able to clearly demonstrate a survival benefit by TIPS. Concordantly, a recent study by Piecha et al. demonstrated that transplant-free survival after TIPS insertion was higher in patients with a lower paracentesis frequency before TIPS placement,[48] supporting our postulation that patients should be considered earlier for TIPS. However, it is important to acknowledge that our data also indicate that CHE < 2.5 kU/L should not be considered as an absolute contraindication for TIPS placement. TIPS patients with baseline CHE < 2.5 kU/L had a similar survival as compared to patients treated with paracentesis, while TIPS insertion may still reduce the need for paracentesis, which has obvious benefits.

In the past, most TIPS studies investigated particular risk factors with regard to their impact on the outcome in a cohort of patients undergoing TIPS placement. However, what is clinically at least equally relevant is the comparison of outcome between TIPS patients and a control group consisting of non-TIPS patients. We particularly addressed this concern by including propensity score–matched control groups of patients treated with paracentesis. Furthermore, the results from our study cohort were additionally confirmed in an external multicenter validation cohort from high-quality tertiary medical centers, resulting in more generalizable conclusions. However, our study also has some limitations that need to be considered: First, this study was conducted in a retrospective and non-randomized manner. Due to the retrospective nature of the study, some patients were lost to follow-up and thus, the patient numbers for the large time span are rather small. Furthermore, there might be an intrinsic selection bias with regard to the allocation of patients to TIPS versus paracentesis with fitter patients being assigned to the TIPS group. Although the selection bias inherent to non-randomization was corrected for by exclusion of patients with contraindications to TIPS and propensity score matching of the remaining patients, this approach reduced the final sample size, as patients for whom no adequate matching partner was found were excluded from analysis. Finally, we were not able to perform a subgroup analysis of patients receiving a TIPS for secondary prophylaxis of variceal bleeding due to small numbers of patients.

In conclusion, our study indicates that serum CHE activity has reasonable prognostic value in terms of predicting outcome after TIPS insertion. Therefore, CHE activity might be considered as an additional and easily accessible parameter when selecting patients for TIPS placement, thereby facilitating personalized treatment decisions. In this regard, the insertion of a TIPS might be considered earlier in the natural history of liver disease as long as hepatic synthetic capacity is only moderately impaired.

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Author names in bold designate shared co-first authorship.

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