Ammonia Levels After Transjugular Intrahepatic Portosystemic Shunt Insertion Identify Patients at High Risk of Hepatic Encephalopathy

Hepatic encephalopathy (HE) remains the most frequent and relevant complications after the insertion of a transjugular intrahepatic portosystemic shunt (TIPS) in patients with liver cirrhosis.[1] Given that prophylactic treatment is potentially available in the form of lactulose or rifaximin, it would be appealing to identify a group of patients at very high risk for post-TIPS HE in whom primary prophylaxis might be justified. Currently, established risk factors, such as a higher Model for End-stage Liver Disease (MELD) score or sarcopenia, are not very reliable at an individual patient level to establish personalized treatment strategies.[1] Ammonia is the key metabolite involved in the pathophysiology of HE.[2] However, ammonia levels measured before TIPS insertion alone are not useful in identifying high-risk patients. We hypothesized that ammonia levels measured within the first days after TIPS might identify patients at high risk of HE.

This study is part of an ongoing prospective study (NCT05466669) and included consecutive patients receiving a TIPS at the Cirrhosis Center Mainz (Germany) between 2022 and 2024. For this sub-study, a sample size calculation was performed, which is described in the Supplementary Methods. Only patients with one of the following TIPS indications were approached: ascites, failure of secondary prophylaxis after variceal bleeding, or a combination of portal vein thrombosis with ascites (termed others). Patients who required rescue or early TIPS were not included. During the time-period, 116 patients received a TIPS. Of these 33 were excluded (reasons: early TIPS [n = 10], rescue TIPS [n = 7], Budd-Chiari Syndrome without cirrhosis [n = 6], declined participation [n = 5], other reasons [n = 5]). Of these 83 patients, 10 had to be excluded because ammonia levels after TIPS were unavailable for logistical reasons, resulting in a final cohort of 73 patients. All patients were recruited and followed according to a predefined protocol (NCT05466669). Structured follow-up visits were conducted at 1, 3, and 6 months after TIPS insertion.

Patients were followed for the development of overt HE (OHE) and liver transplantation/death after TIPS insertion. At each structured visit 1, 3, and 6 months after TIPS and during unplanned hospitalization, each patient was examined by an experienced hepatologist for the presence of OHE.

Ammonia levels were measured from venous blood following a predefined standard operating procedure that involves rapid sample transport on ice to the central laboratory and measurement within 20 minutes before TIPS insertion and after 3 to 4 days post-TIPS. In a subgroup, ammonia was measured at day 1, 2, and 3/4 post-TIPS to evaluate whether there are kinetics in ammonia levels within the first days after TIPS. The upper limit of normal (ULN) was 72 μmol/L, and ammonia levels were normalized to the ULN. Additionally, patient groups were dichotomized according to the ULN.

The study was approved by the ethics committee of the Landesärztekammer Rheinland-Pfalz (Nr.2021-16247_1). Written informed consent was obtained from all participants. The study was carried out according to the principles of the Declaration of Helsinki.

Information on the TIPS insertion procedure, testing for covert HE (CHE) and statistics are provided in the Supplementary Methods.

Characteristics before TIPS insertion are displayed in Supplementary Table 1. Additionally, a comparison between patients with ammonia levels post-TIPS (ammon-post-TIPS) above and below the ULN is also presented in Supplementary Table 1. In a sub-analysis of 14 consecutive patients, we found that ammonia levels (in μmol/L) mostly increased until day 3/4, and therefore we decided to stick to our hypothesis to measure ammonia at day 3 or 4 after TIPS in all patients (Figure 1*A*). During a median follow-up of 127 days (interquartile range [IQR], 54–323 days), 33 patients (45%) developed an OHE episode (grade 2, n = 21; grade 3, n =11; grade 4, n = 1). Of these, 91% occurred during the first three months after TIPS insertion. Additionally, 19 patients (26%) died or received a liver transplantation. In univariable analyses, ammon-post-TIPS above the ULN (72 μmol/L) was associated with the development of OHE in the total cohort as well as in the subcohort of patients with ascites as TIPS indication (Figure 1*B* and *C*; Supplementary Table 2). Of note, ammonia levels pre-TIPS were not associated with post-TIPS HE

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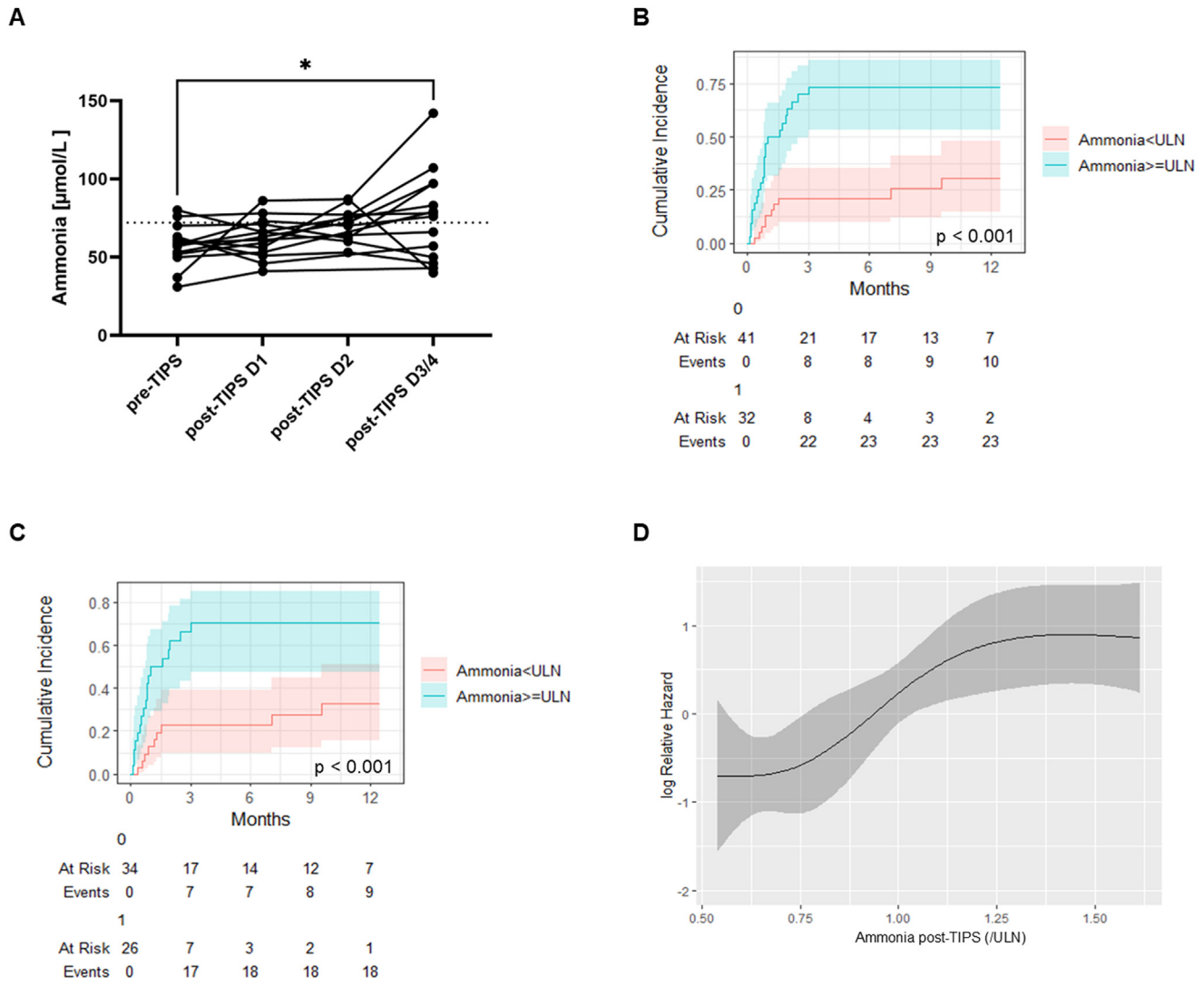

Fig. 1. Trajectory of ammonia levels and cumulative overt HE (OHE) incidence stratified by ammonia levels. (*A*) The trajectory of ammonia levels in 14 consecutive patients before and at days 1, 2, and 3/4 after TIPS insertion. (*B*/*C*) Cumulative OHE incidences in the total cohort stratified by the ammonia post-TIPS upper limit of normal (ULN) (*B*) or the subcohort with ascites as indication for TIPS (*C*). (*D*) The non-linear effect of ammonia post-TIPS (/ULN) on post-TIPS HE risk. *$P < .05$.

(Supplementary Table 2). Moreover, 12 of 19 patients with a history of OHE developed post-TIPS HE (63%). Non-linear effects of ammon-post-TIPS on the risk of post-TIPS HE are displayed in Figure 1*D*. In multivariable regression analysis, ammon-post-TIPS as a continuous variable (normalized to the ULN of 72 μmol/L) (subdistribution hazard ratio [sHR], 2.55; 95% confidence interval [CI], 1.14–5.67; $P = .022$) or dichotomized according to the ULN (sHR, 3.68; 95% CI, 1.72–7.85; $P < .001$) remained independently associated with post-TIPS HE after adjusting for MELD, portosystemic gradient (PSG) decrease in percent, and history of OHE (Supplementary Table 2). Time-dependent discriminative ability of ammon-post-TIPS to identify patients with post-TIPS HE within 180 days was good (area under the curve [AUC], 0.82 at day 180) and significantly better at all time-points than MELD (AUC, 0.67 at day 180), C-reactive protein (CRP) (AUC, 0.42 at day 180), white blood cell count (AUC, 0.34 at day 180), or interleukin-6 (AUC, 0.56 at day 180) (each $P < .001$ vs ammon-post-TIPS). In Cox regression analysis adjusting for MELD (hazard ratio [HR], 1.17; 95% CI, 1.04–1.31; $P = .008$), ammon-post-TIPS was not associated with a higher risk of death or need for liver transplantation (HR, 1.69; 95% CI, 0.65–4.38; $P = .3$).

In this study, we demonstrate for the first time that ammonia measured at day 3 or 4 after TIPS insertion is an excellent and readily available biomarker identifying patients at high risk for post-TIPS HE. In our cohort, 3 of 4 patients exceeding the ULN of ammonia suffered from an OHE episode during follow-up, mostly within the first 3 months. Using ammonia measurements after TIPS insertion might enable the implementation of personalized treatment strategies in this highly vulnerable patient group.

In recent years, ammonia has experienced a rebirth as a biomarker in patients with cirrhosis. Large multicenter studies demonstrated a robust association between higher

ammonia levels and death in the outpatient setting.[3–5] Additionally, the same group found ammonia to be a key biomarker in a score predicting OHE in outpatients with cirrhosis.[6] Our study is in line with these findings by demonstrating that ammonia measured after TIPS insertion and not before TIPS is highly useful for identifying patients at risk for OHE. The pathophysiologic explanation for this finding might be that ammonia homeostasis is dramatically changed by TIPS insertion; however, the severity of the change in ammonia metabolism is not predictable.

In conclusion, our study provides evidence that ammonia measured on day 3 or 4 after TIPS insertion is an excellent and readily available biomarker identifying patients at high risk for post-TIPS HE. Measuring ammonia might enable personalized treatment strategies in patients after TIPS insertion.

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2025.03.011.

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Data Availability
All raw data are available from the corresponding author on reasonable request.

Supplementary Methods

Transjugular intrahepatic portosystemic shunt (TIPS) insertion was performed at the Department of Diagnostic and Interventional Radiology according to an institutional standard operating procedure. Insertion was conducted under general anesthesia using polytetrafluoroethylene-covered stent grafts (GORE VIATORR TIPS Endoprosthesis). Measurement of the portosystemic pressure gradient (PPG) was conducted in accordance with the recommendations of the BAVENO VII consensus.[1] At the time of insertion of the TIPS, we aimed for a target PPG of $<$12 mm Hg, and the TIPS diameter was adjusted accordingly. A second measurement of the PPG was conducted after 2 to 3 days (but before the post-TIPS ammonia measurement) under local anesthesia to avoid confounding by sedation. If the PPG was above 12 mm Hg at the second measurement, then the TIPS was further dilated.

Testing for covert hepatic encephalopathy (CHE) was done using the portosystemic encephalopathy (PSE) syndrome test, which yields the psychometric hepatic encephalopathy score (PHES). Interpretation of PHES was done according to German norms.[2] A score <-4 was considered pathologic.

Given that no study has previously investigated the risk of post-TIPS overt hepatic encephalopathy (OHE) in patients with ammonia levels post-TIPS below or above the upper limit of normal (ULN), we had to estimate potential event rates for a sample size calculation and also chose an event-driven approach. Given that the post-TIPS OHE rate ranges between 20% and 50%,[3] we expected an overall event rate of about 35% for our cohort. Furthermore, we assumed an increased event rate of 45% in patients with ammonia levels above the ULN and a decreased event rate of 20% in patients with levels below the ULN. This results in 33 events that have to be observed to sufficiently detect a significant difference between both groups with 80% power and a 2-sided significance level of .05.[4]

Data were analyzed using R 4.3.3, RStudio version 2023.12.1.402 and GraphPad Prism Version 8.0.2. We present categorical data as numbers with percentages and continuous data as median with interquartile range (IQR). Pairwise comparisons between patients with ammonia levels above or below the ULN were performed with the χ^2 test, Wilcoxon rank sum test, or the Fisher exact test, as appropriate. Comparisons between paired groups (longitudinal ammonia levels) were performed using Friedman's test.

The {tidycmprsk} R package was used for both cumulative incidence functions for competing risk analyses, and Fine and Gray competing risk regression analyses. The coding for the multi-state models with 3 states for OHE development analysis was: 0: alive without liver transplantation and no OHE event at the end of follow-up; 1: OHE event during follow-up; and 2: death or liver transplantation without prior OHE event during follow-up. This means that death or liver transplantation prior to an OHE event were treated as competing events. Due to the number of events, we preselected variables for inclusion in the multivariable model according to mechanistic plausibility. We therefore included ammonia post-TIPS, Model for End-stage Liver Disease (MELD), PSG decrease in percent, and history of OHE.

To assess the non-linear effects of ammonia post-TIPS on OHE development, ammonia levels were fitted using restricted cubic splines with 4 knots in a Cox model ({rms}R package).

Time-dependent area under the curve (AUC) analyses of the receiver operating characteristic curves for prediction of post-TIPS OHE under consideration of the competing events (death/liver transplantation) were conducted using the {timeROC} R package.

For liver transplantation-free survival analysis, a Cox proportional hazards regression model was built. Here, a 2-state model with death and liver transplantation as composite endpoints was used (0: alive, not transplanted; 1: dead or liver transplanted). Due to the number of events, we included ammonia post-TIPS and MELD in the final model.

To define statistically relevant deviations from the respective null hypothesis, we used a .05 level.

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Supplementary Table 1. Baseline Characteristics and Comparisons of Study Cohort Characteristics Stratified by Ammonia Post-TIPS ULN

Variable	N	Total cohort (N = 73)	Ammonia post-TIPS < ULN (n = 41)	Ammonia post-TIPS ≥ULN (n = 32)	*P* value
Age, *y*	73	61 (54–65)	60 (49–64)	64 (58–68)	**.041**
Sex	73				.9
Male		51 (70)	29 (71)	22 (69)	
Female		22 (30)	12 (29)	10 (31)	
Etiology	73				.2
ALD		38 (52)	26 (63)	12 (38)	
MetALD		1 (1.4)	0 (0)	1 (3.1)	
MASLD		13 (18)	6 (15)	7 (22)	
Viral		7 (9.6)	3 (7.3)	4 (13)	
Other		12 (16)	6 (15)	6 (19)	
ALD + viral		2 (2.7)	0 (0)	2 (6.3)	
Indication for TIPS	73				>.9
Ascites		60 (82)	34 (83)	26 (81)	
Secondary prophylaxis after bleeding		9 (12)	5 (12)	4 (13)	
Other		4 (5.5)	2 (4.9)	2 (6.3)	
Child-Pugh	73				.5
A		6 (8.2)	2 (4.9)	4 (13)	
B		55 (75)	31 (76)	24 (75)	
C		12 (16)	8 (20)	4 (13)	
MELD score	73	14.0 (10.0–17.0)	12.0 (10.0–16.0)	14.5 (11.0–17.0)	.12
FIPS score	73	0.14 (−0.54 to 0.55)	−0.07 (−0.77 to 0.26)	0.36 (−0.38 to 0.61)	**.026**
PSG delta, %	73	58 (50–68)	57 (50–65)	61 (54–69)	.2
TIPS diameter, *mm*	73				.15
6		2 (2.7)	0 (0)	2 (6.3)	
7		1 (1.4)	1 (2.4)	0 (0)	
8		35 (48)	18 (44)	17 (53)	
9		1 (1.4)	0 (0)	1 (3.1)	
10		34 (47)	22 (54)	12 (38)	
PHES	61	−4.0 (−7.0 to −2.0)	−3.5 (−6.5 to −1.0)	−7.0 (−10.0 to −2.0)	.068
History of OHE	73	19 (26)	9 (22)	10 (31)	.4
Sodium, *mmol/L*	73	136.0 (134.0–138.0)	136.0 (134.0–138.0)	136.0 (134.5–138.5)	.5
Creatinine, *mg/dL*	73	1.21 (0.93–1.61)	1.13 (0.88–1.50)	1.35 (1.03–1.97)	**.041**
Bilirubin, *mg/dL*	73	1.10 (0.80–1.60)	1.10 (0.70–1.60)	1.10 (0.80–1.60)	.9
Albumin, *g/L*	73	31.0 (28.0–35.0)	31.0 (27.0–35.0)	32.0 (29.5–38.0)	.12
CRP, *mg/L*	73	8 (4–15)	8 (5–18)	8 (3–15)	.6
Interleukin 6, *pg/mL*	66	22 (13–49)	17 (13; 38)	46 (14–61)	**.046**
WBC, *per nL*	73	5.30 (3.70–7.70)	5.90 (4.30–8.20)	4.20 (3.05–6.15)	**.028**
Hemoglobin, *g/dL*	73	10.50 (9.00–12.00)	11.00 (9.40–12.30)	10.10 (8.25–11.30)	**.031**
Platelets, (per nL)	73	112 (72–172)	128 (74–206)	99 (64–163)	.2
Ammonia pre-TIPS, *μmol/L*	69	52 (41–61)	52 (37–74)	52 (42–59)	.8
Ammonia pre-TIPS above the ULN	69	13 (19)	10 (26)	3 (10)	.10
Ammonia post-TIPS, *μmol/L*	73	66 (50–82)	52 (43–58)	84 (77–101)	**<.001**
Ammonia post-TIPS (/ULN)	73	66 (50–82)	0.72 (0.60–0.81)	1.17 (1.07–1.40)	**<.001**
Ammonia delta, *μmol/L*	69	14 (−3 to 29)	1 (−15 to 12)	36 (21–56)	**<.001**

Supplementary Table 1. Continued

Variable	N	Total cohort (N = 73)	Ammonia post-TIPS < ULN (n = 41)	Ammonia post-TIPS ≥ULN (n = 32)	*P* value
Ammonia delta, %	69	31 (−5 to 74)	2 (−17 to 30)	76 (36–125)	**<.001**
Lactulose use	73	42 (58)	23 (56)	19 (59)	.8
Rifaximin use	73	11 (15)	6 (15)	5 (16)	>.9

NOTE. Data are expressed as median with interquartile range or as number with percentages.
NOTE. Boldface P values indicate statistical significance.
ALD, alcohol-related liver disease; CHE, covert hepatic encephalopathy; CRP, C-reactive protein; FIPS, Freiburg index for post-TIPS survival; MASLD, metabolic dysfunction associated liver disease; MELD, Model for End-stage Liver Disease; metALD, MASLD and increased alcohol intake; PHES, psychometric hepatic encephalopathy score; PSG, portosystemic gradient; TIPS, transjugular intrahepatic portosystemic shunt; ULN, upper limit of normal; WBC, white blood cell count.

Supplementary Table 2. Univariable and Multivariable Fine and Gray Regression Analysis for Post-TIPS OHE Development

		Univariable analysis			Multivariable analysis			Multivariable analysis		
Characteristic	N	sHR	95% CI	*P* value	sHR	95% CI	*P* value	sHR	95% CI	*P* value
Age, *y*	73	1.04	1.01–1.07	.009						
Female sex	73	1.22	0.60–2.49	.6						
PSG delta, %	73	1.01	0.99–1.03	.4	1.01	0.98–1.04	.6	1.01	0.98–1.04	.6
TIPS diameter, *mm*	73	1.09	0.81–1.47	.6						
MELD	73	1.07	0.99–1.15	.074	1.04	0.97–1.13	.3	1.04	0.97–1.12	.3
FIPS	73	1.77	1.14–2.64	.010						
History of OHE	73	2.37	1.16–4.87	.018	1.81	0.82–4.02	.14	1.78	0.81–3.90	.2
PHES	61	0.85	0.74–0.96	.007						
Sodium, *mmol/L*	73	0.97	0.91–1.04	.5						
Creatinine, *mg/dL*	73	1.59	1.08–2.36	.020						
Bilirubin, *mg/dL*	73	0.92	0.63–1.34	.7						
Albumin, *g/L*	73	0.99	0.94–1.04	.7						
CRP, *mg/L*	73	0.99	0.96–1.01	.3						
WBC, *per nL*	73	0.85	0.73–0.99	.039						
Hemoglobin, *g/dL*	73	0.76	0.66–0.88	<.001						
Platelets, *per nL*	73	1.0	0.99–1.00	.020						
Ammonia pre-TIPS, */ULN*	69	1.93	0.75–4.95	.2						
Ammonia post-TIPS, */ULN*	73	3.48	1.74–6.96	<.001	2.55	1.14–5.67	.022			
Ammonia post-TIPS above the ULN (dichotomized)	73	4.24	2.05–8.75	<.001				3.68	1.72–7.85	<.001
Ammonia delta (post-TIPS – pre-TIPS, %)	69	1.01	1.00–1.01	.005						
Lactulose	73	1.53	0.74–3.18	.3						
Rifaximin	73	1.04	0.42–2.56	.9						

NOTE. In univariable Fine and Gray regression for OHE development, liver transplantation and death were treated as competing events.
CI, confidence interval; CRP, c-reactive protein; FIPS, Freiburg index for post-TIPS survival; MELD, model for end-stage liver disease; OHE, overt hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; PSG, portosystemic gradient; sHR, subdistribution hazard ratio; ULN, upper limit of normal; WBC, white blood cell count.