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Covert hepatic encephalopathy and spontaneous portosystemic shunts increase the risk of developing overt hepatic encephalopathy

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Abstract

Aim: The aim of the study was to evaluate the presence of covert hepatic encephalopathy (cHE) and its characteristics according to the presence of spontaneous portosystemic shunts (SPSS) and their influence on the development of overt hepatic encephalopathy.

Methods: Secondary analysis of a multicentre study, which evaluated the association between SPSS and complications of cirrhosis. The present study population includes those patients who also underwent cHE diagnostic evaluation. Presence of SPSS was evaluated by cross-sectional imaging and quantified by total SPSS-area. Logistic and Cox-regression competing risk analyses were performed.

Results: About 65 patients were included of age 58 (IQR 50-66), MELD 15 (IQR 10-20), with alcoholic liver disease 63%. Thirty-two patients (49%) had cHE, had higher MELD [16 (IQR 12-24) vs 13 (IQR 9-17), $P = .027$], a greater proportion of SPSS [n = 18 (56%) vs n = 8 (24%); $P = .008$] and a higher total cross-sectional SPSS-area [28.3 (0-94.2) vs 0 (0-14.1); $P = .005$]. On multivariate analysis MELD [OR 1.11 (95% CI 1.01-1.21)] and presence of SPSS [OR 3.95 (95% CI 1.22-12.80)] were independently associated to cHE at baseline. During follow-up cHE was an independent predictor of oHE [cHE: HR 6.93 (95% CI 2.64-18.20). The effect of cHE on the development of oHE was greater in patients with SPSS [only cHE: HR 5.66 (95% CI 1.82-17.62), cHE and SPSS: HR 8.63 (95% CI 3.15-23.65)].

Conclusions: cHE is independently associated to the presence of SPSS (and total cross-sectional SPSS-area) and MELD. Furthermore, the presence of SPSS seems to increase the risk of cHE of developing of overt hepatic encephalopathy.

KEYWORDS

cirrhosis, complications, hepatic encephalopathy, spontaneous portosystemic shunts

Abbreviations: CFF, critical flicker frequency; cHE, covert hepatic encephalopathy; HE, hepatic encephalopathy; HR, hazard ratio; IQR, interquartile range; MRI, magnetic resonance imaging; oHE, overt hepatic encephalopathy; OR, odds ratio; PHES, psychometric hepatic encephalopathy score; SBP, spontaneous bacterial peritonitis; SPSS, spontaneous portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt; TSA, total SPSS area.

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1 | INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric disorder that presents with a broad spectrum of cognitive and neuromuscular impairment. Covert hepatic encephalopathy (cHE) is the mildest stage and includes both minimal HE and grade I HE.[1] In this stage of the disease, patients characteristically show only subtle and difficultly recognizable abnormalities without obvious disorientation nor asterixis. cHE is highly prevalent in cirrhosis (up to 60%[2,3]) and leads to multiple negative consequences such as reduced quality of life,[4-6] falls[7] and vehicle accidents[8] and increased progression to the overt form of the disease (overt HE),[9,10] which in turn is associated to a high mortality.[11]

Accumulation of toxic metabolites, mainly ammonia, play a major role in the development of hepatic encephalopathy. These metabolites are able to pass the blood-brain barrier and negatively affect glioneural communication.[12] Patients with cirrhosis have typically a high concentration of potentially toxic metabolites, because of hepatic insufficiency, spontaneous portosystemic shunts or a combination of both.

The formation of spontaneous portosystemic shunts (SPSS) in patients with cirrhosis is mainly a consequence of portal hypertension. These shunts develop in an attempt to reduce portal pressure, however, this attempt remains ultimately insufficient.[13,14] A recent study has shown that 60% of patients with cirrhosis have SPSS, and their prevalence increases with worsening liver function.[15] The presence of SPSS in patients with cirrhosis and their size is associated to the development of overt hepatic encephalopathy (oHE) in its recurrent or persistent form.[14-17] Besides from being associated to HE, SPSS and also their calculated total SPSS area (TSA) are linked to the occurrence of other portal hypertension-associated complications like bleeding and ascites; and are an independent predictor of mortality.[15,16,18] The association of SPSS to covert hepatic encephalopathy (cHE: minimal HE and grade I) in patients with cirrhosis and their effect on the development of oHE remain unknown. Therefore, the aims of the present study were to determine the prevalence and characteristics of cHE in cirrhotic patients according to the presence or absence of SPSS and their influence on the development of oHE.

Key points

Covert hepatic encephalopathy is a mild/subclinical alteration of mental status in cirrhosis. The presence of shunts between the portal venous system and systemic venous system is characteristic of cirrhosis. Patients with these shunts have increased likelihood of covert hepatic encephalopathy. Covert hepatic encephalopathy increases the risk of clinical manifest altered mental status (overt hepatic encephalopathy), a complication of cirrhosis with prognostic implications. When shunts are present, the risk of overt hepatic encephalopathy in patients with covert hepatic encephalopathy seems greater.

2 | PATIENTS AND METHODS

This study is a secondary analysis of a subgroup of patients included in a multicentre study that examined the associations of SPSS and complications of cirrhosis including mortality.[15] The inclusion and exclusion criteria have been previously described extensively. Briefly, patients were included if they had cirrhosis, were older than 18 years and underwent a contrast-enhanced abdominal computed tomography or an abdominal magnetic resonance imaging (MRI) for any reason between 2010 and 2014. If available, the calculated shunt size was preferably based on CT imaging technique rather than MR imaging. Diagnosis of cirrhosis was based on medical history and on a combination of clinical, laboratory, abdominal imaging (ultrasound, CT, MRI), endoscopic and histological findings. Patients with hepatocellular carcinoma beyond Milan criteria, a surgical shunt or previous transjugular intrahepatic portosystemic shunt (TIPS) and any medical condition with a life expectancy lower than 6 months were excluded.

For the present study, patients were included if testing for cHE was performed. All centres were contacted regarding participation in the substudy. Patients with cognitive disorders preventing a correct cHE-evaluation, and HE ≥ grade 2 at the point of cHE-testing were excluded. Two centres which had participated in the initial study had data regarding cHE [Martin-Luther-University Halle-Wittenberg (Halle, Germany) and Vall d'Hebron University Hospital, (Barcelona, Spain)]. Patients with a difference greater than 90 days between cHE testing and imaging procedure (before or after inclusion) were excluded from the analysis (n = 26). The median delay between the performance of cHE testing and inclusion in the original study was 3 days (IQR −14 to 39): Halle 1 day (IQR −23 to 6) and Vall d'Hebron 47 days (IQR 37-65) days.

Patients who fulfilled the inclusion criteria and had no exclusion criteria had their medical history reviewed and were included in the analysis. Demographic characteristics, aetiology of liver disease, comorbidities, previous complications of cirrhosis and laboratory and further clinical parameters were collected at baseline. A flow chart showing patient inclusion in this secondary analysis of the multicentre SPSS-study[15] is displayed in Figure 1.

Follow-up was performed until the 31th of December 2015, liver transplantation or death. Patients who were lost to follow-up were censored at their last visit. All complications of end-stage liver disease were registered, including overt HE (≥2 grade HE with hospitalization); ascites, gastrointestinal bleeding caused by portal-hypertension, spontaneous bacterial peritonitis (SBP) and other infections.

2.1 | Evaluation of cognitive function and diagnosis of covert HE

The diagnostic tests used for the evaluation of cognitive function were the determinants of the critical flicker frequency (CFF) and

a psychometric test battery composed of five different tests—the Portosystemic-Encephalopathy-Syndrome (PSE) test.

2.1.1 | Portosystemic-Encephalopathy-Syndrome test

The PSE is a selection of five different tests especially developed to detect classic cognitive impairments in HE.[19] Briefly, it comprises five different tests: the number connection test-A, the number connection test-B, the digital symbol test, the line-tracing test and the serial dotting test. The score on each single test depends on the performance and ranges from 1 to −3. The composite score of all five tests is called PHES. In Germany and Spain, the test has been validated and norm data from their populations are available.[20,21] A score lower than −4, suggests the presence of cHE in these populations.

2.1.2 | Critical flicker frequency

The CFF is determined with an electronic device that shows patients a flickering light, which progressively lowers its frequency in a specific time interval. The patients have to identify the frequency at which the light is first perceived as flickering—this frequency is the CFF. Determination of CFF was performed using Hepatonorm Analyzer Version 2.0 (R&R Medi-Buisness Freiburg, Germany). After a brief instruction, the patients underwent an initial training phase in which premeasurements were done to get the patients used to the procedure. Once the patients were familiar with the test, eight measurements were performed in the measurement phase. The mean value of these measurements was calculated. Lower values indicate greater cortical dysfunction. CFF with a cut-off of 39 Hz was used to define which patients had a pathological test.

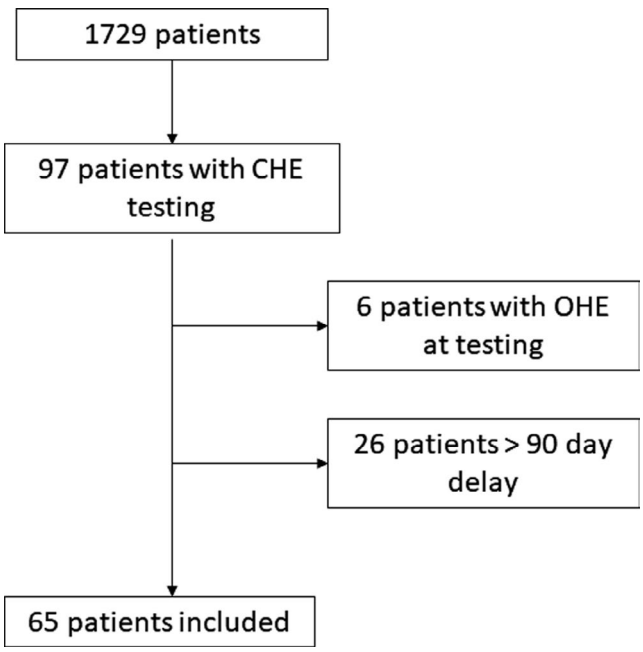

FIGURE 1 Flow chart of patient inclusion in the secondary analysis of the multicentre SPSS-study.[15] cHE-covert hepatic encephalopathy, OHE-overt hepatic encephalopathy, SPSS-spontaneous portosystemic shunt

2.1.3 | Definition of covert hepatic encephalopathy

cHE was defined by abnormal age-corrected PHES (<−4) and lack of overt hepatic encephalopathy (≥ grade 2) as determined clinically.

2.2 | Radiological data and calculation of shunt area

Abdominal CT and MRI were examined for the presence of SPSS by a radiologist with expertise in hepatic disease in both study centres. SPSS were defined as spontaneous communications between the portal venous system or splanchnic veins and the systemic venous system, excluding gastroesophageal varices. The radius of each detected SPSS was measured to calculate the cross-sectional area. The sum of all cross-sectional SPSS areas (mm^2) was obtained (TSA: total SPSS area).[16] All shunt sizes were potentially included in this study, however in order for the calculation to be technically feasible, a shunt diameter of at least 5 mm is needed to provide an accurate TSA-calculation. The smallest shunt included in this study was 6 mm. Patients without SPSS were assigned a TSA of 0 mm^2.

The diameters of the SPSS were measured twice in the previous studies. The initial data from Simón-Talero et al[15] were reviewed again by the same expert radiologists for the following study from Praktiknjo et al.[16] For the latter study, the intra-observer variability of the measurement was calculated, with an intraclass correlation coefficient of 0.95 (95% CI 0.94-0.96).[16]

2.3 | Statistical analysis

Data were processed in SPSS version 22.0 and SAS version 9.4. Data are described with proportions or medians (interquartile range: IQR). Chi-square test, Student *t* or *U*-Mann Whitney were used according to variable distribution. There are no missing data concerning the main variables (PHES, CFF, Presence of SPSS, TSA). Univariate analysis was used to identify the variables associated to covert hepatic encephalopathy as defined by the PHES (see above) with specific focus on the presence of portosystemic shunts. The main analysis was done according to the presence or absence of shunts, however, in order to achieve further granularity, further analysis was performed with the TSA introduced as a continuous variable. Backward stepwise multivariate logistic regression analysis was performed to evaluate independent predictors of covert hepatic encephalopathy. Univariate Cox-regression analysis was done to evaluate the incidence of complications of cirrhosis according to the presence of cHE. Univariate and backward stepwise multivariate Cox regression analysis was done to evaluate predictors of oHE during follow-up.

Backward stepwise multivariate Cox regression competing risk analysis (Fine and Gray 1999) was performed to evaluate the effect of SPSS and cHE on the development of oHE during follow-up. Competing risks were liver transplantation and death. Models were constructed in order to avoid inclusion of variables with redundant information (i.e MELD and hepatorenal syndrome). Graphical evaluation of risk groups was done with cumulative incidence curves. Institutional review board approval for the present study was obtained (2016-36).

3 | RESULTS

3.1 | Baseline characteristics and previous complications

A flow chart of patient inclusion is shown in Figure 1. A total of 65 patients (Halle n = 50; Barcelona n = 15) who met the inclusion criteria and did not have any exclusion criteria formed the study population. Baseline characteristics and previous decompensating events of included patients are shown in Table 1. Median age was 58 (IQR 50-66) years. The majority of patients had alcohol-associated liver disease and was predominantly male. The whole spectrum of severity of liver disease was represented, although most patients had advanced stages of the disease (more than 75% of patients had at least Child-Pugh class B). In comparison to the original study, the patients included in the present study were sicker as shown by higher MELD and Child-Pugh grade. Furthermore, patients included in the present study had more frequently alcohol-associated liver disease (See Table S1). cHE, determined by PHES, was diagnosed in almost half of the study population (49%). Factors associated with cHE are shown on Table 1. No significant differences in medication (diuretics, ß-blocker, rifaximin/neomycin and disaccharides), severity of liver disease as estimated by Child-Pugh class and biochemical parameters were observed between the two study groups (cHE and No HE). Nevertheless, patients with cHE had significantly higher MELD [16 (12-24) vs 13 (9-17); $P = .027$] and had had more frequently previous complications of cirrhosis, most importantly more patients had experienced previous HE (63% vs. 24%; $P = .003$). Not unexpectedly, patients with cHE displayed a lower CFF (37.2 Hz vs. 40.3 Hz; $P = .002$).

At least one SPSS was detected in 40% of patients of the whole group. Patients with cHE had more often SPSS (56% vs 24%; $P = .008$) and therefore a greater TSA [28.3 mm^2 (0-94.2) vs 0 mm^2 (0-14.1); $P = .005$]. Indeed, TSA correlated with PHES ($r = -0.376$; $P = .002$). The majority of SPSS were splenorenal and paraumbilical (see Table 2). Although the sample size precluded drawing robust conclusions, patients with cHE with and without shunts were compared. Interestingly and although not statistically significant, patients with cHE without shunts had more severe hepatic dysfunction as shown by greater bilirubin [1.9 mg/dL (1.23-3.1) vs 3.11 mg/dL (1.23-8.25) $P = .512$] and lower creatinine as an indirect marker of greater sarcopenia [0.95 mg/dL (0.75-1.28) vs 1.18 mg/dL (0.90-2.00), p value = 0.077].

3.2 | Independent predictors of covert hepatic encephalopathy

To evaluate the independent predictors of cHE including SPSS, we performed a multivariate analysis with the significant factors identified in the univariate analysis (MELD, presence of SPSS or TSA, prior oHE and prior SBP). MELD (OR, 1.11; 95% CI, 1.01-1.21) and the presence of SPSS (OR, 3.95; 95% CI, 1.22-12.80) were identified as independent predictors (see Table 3). If TSA was introduced as a continuous variable in the model instead of SPSS: MELD, prior SBP and TSA (OR, 1.01; 95% CI, 1.00-1.02; $P = .046$) were identified as independent predictors (see Table 3).

4 | FOLLOW-UP

The median follow-up was 5 months (IQR 2-18). Patients with cHE developed complications of liver disease more frequently than patients without cHE (see Table 4). During follow-up, 37% of the study cohort developed oHE. Not unexpectedly, on univariate survival competing risk analysis cHE was associated to the development of oHE during follow-up [HR 7.21 (95% CI 2.73-19.04)] (Figure 2). There was a trend to a greater incidence of oHE among patients with SPSS, although this was not statistically significant [HR 1.92 (95% CI 0.88-4.17)] (Figure 3). Interestingly, no patient with SPSS without cHE at baseline developed oHE during follow-up (n = 8). On bivariate analysis, only cHE was an independent predictor of oHE during follow-up [cHE: HR 6.93 (95% CI 2.64-18.20); SPSS: HR 1.15 (95% CI 0.54-2.43)]. However, when the patients were divided according to the sole presence of cHE and the presence of cHE and SPSS, the magnitude of the effect of cHE on the development of oHE was greater in patients with SPSS, suggesting that the presence of SPSS could modulate the effect of cHE [only cHE HR 5.66 (95% CI 1.82-17.62), and cHE and SPSS with HR 8.63 (95% CI 3.15-23.65) compared to patients without cHE] (Figure 4). Univariate and multivariate Cox-regression analysis of predictors of oHE during follow-up is provided in the Tables S2 and S3 respectively.

4.1 | CFF - association to SPSS and prognostic value

CFF was not associated with the presence of SPSS ($P = .241$) nor to TSA ($r = -0.159$, $P = .205$). No association between SPSS and cHE diagnosed by CFF was observed [using both the classical (39 Hz) or the alternative (38 Hz) CFF-cut-off] ($P = .156$ and $P = .298$). CFF at baseline was not associated with the development of complications during follow-up including oHE [CFF HR 0.94 (95% CI 0.86-1.03), $P = .158$].

TABLE 1 Baseline characteristics, previous decompensations and current medication of all patients and subgroups with covert HE and No HE

Patient Characteristics	All n = 65 (100%)	No HE n = 33 (51%)	covert HE n = 32 (49%)	*P*-value
Age	58 (50-66)	57 (50-65)	59 (47-67)	.728
Sex (male) in %	65	64	66	.867
Aetiology				.563
Alcohol-induced	41 (63%)	19 (58%)	22 (69%)	
Viral	5 (8%)	3 (9%)	2 (6%)	
NASH	2 (3%)	2 (6%)	0 (0%)	
Cryptogenic	3 (5%)	2 (6%)	1 (3%)	
Combined	6 (9%)	4 (12%)	2 (6%)	
Others	8(12%)	3 (9%)	5 (16%)	
Severity of liver disease				
Child-Pugh-Class				.506
A	15 (23%)	9 (28%)	6 (19%)	
B	27 (42%)	14 (44%)	13 (41%)	
C	22 (34%)	9 (28%)	13 (41%)	
MELD	15 (10-20)	13 (9-17)	16 (12-24)	**.027**
Prior HE	35/64 (47%)	9 (27%)	20/31 (63%)	**.003**
GI haemorrhage	13/62 (20%)	8 (24%)	5/29 (16%)	.499
Ascites	51/63 (79%)	24/32 (73%)	27/31 (85%)	.081
SBP	9/61 (14%)	2/32 (6%)	7/29 (22%)	**.049**
HRS	5/59 (8%)	1 (3%)	5/27 (16%)	**.011**
HCC	6/64 (99%)	4 (12%)	2/31 (6%)	.437
Esophageal varices	50/62 (81%)	25/32 (78%)	25/30 (83%)	.525
Medication%				
Lactulose or Lactitol	34 (52%)	14 (42%)	20/31 (63%)	.077
Rifaximin or neomycin	2/62 (3%)	2/32 (6%)	0/31 (0%)	.368
Diuretics	51 (79%)	26 (79%)	25 (78%)	.948
ß-Blockers	39/64 (60%)	21 (64%)	18/31 (56%)	.648
covert HE testing		.		
CFF	38.9 (36.5-41.7)	40.3 (38.0-43.8)	37.2 (35.7-39.9)	**.002**
PHES	-4 (−10 - −1)	-1 (−2-0)	-10 (−15-−6)	**.0001**
SPSS				
Prevalence of SPSS	26 (40%)	8 (24%)	18 (56%)	**.008**
SPSS total area in mm^2	0 (0-66.1)	0 (0-14.1)	28.3 (0-94.2)	**.005**
Biochemistry parameters				
Bilirubin (mg/dL)	1.97 (1.11-3.74)	1.97 (0.99-3.16)	1.93 (1.23-6.39)	.262
INR	1.4 (1.2-1.7)	1.4 (1.2-1.6)	1.4 (1.3-1.8)	.315
Creatinine (mg/dL)	0.99 (0.86-1.25)	0.96 (0.87-1.11)	1.06 (0.81-1.58)	.162
Sodium (µmol/L)	136 (133-139)	136 (134-138)	137 (131-140)	.622
Albumin (g/dL)	2.8 (2.4-3.1)	2.9 (2.4-3.3)	2.7 (2.3-3.1)	.468
Haemoglobin (g/dL)	11.0 (10.1-12.6)	10.8 (10.2-12.3)	11.4 (9.6-12.6)	.555
Platelets × $10^3/mm^3$	113 (71-154)	112 (78-194)	117 (65-147)	.379

Note: Significant p-values are displayed in bold. The denominator is the number of patients included in each column unless otherwise specified.

Abbreviations: CFF, critical flicker frequency; GI, gastrointestinal: HCC, hepatic cell carcinoma; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; PHES, psychometric hepatic encephalopathy score; SBP, spontaneous bacterial peritonitis, SPSS, spontaneous portosystemic shunt; TSA, total cross-sectional SPSS area.

TABLE 2 Distribution of SPSS in all patients and in the subgroups with No HE and covert HE

Type of SPSS	All (n = 38)	No HE (n = 10)	covert HE (n = 28)
Splenorenal	16 (42%)	5 (50%)	11 (39%)
Paraumbilical	15 (39%)	4 (40%)	11 (39%)
IMV caval	4 (11%)	1 (10%)	3 (11%)
Mesocaval	1 (3%)	0	1 (4%)
Others	2 (5%)	0	2 (7%)

Note: Some patients have more than one SPSS.

Abbreviations: HE, hepatic encephalopathy; IMV, inferior mesenteric vein.

5 | DISCUSSION

This study shows an association between the presence of subclinical cognitive dysfunction (cHE) and the presence of shunts and their size, as measured by the TSA. Furthermore, the impact of cHE and SPSS in the natural history of cirrhosis has been evaluated; indeed, patients with both entities have an almost ninefold increase in the incidence of overt hepatic encephalopathy during follow-up.

The association of portosystemic shunts and overt HE has been established since decades. Presence of portosystemic shunts has been associated with persistent hepatic encephalopathy [17] and embolization of large portosystemic shunts has been described as a possible therapeutic option in patients with therapy refractory overt hepatic encephalopathy and low MELD score.[22] Recently, a large multicentre cohort study has characterized portosystemic shunts in patients with cirrhosis and observed an association between the presence of large shunts (over 8 mm) with the development of overt hepatic encephalopathy during follow-up.[15]

Large portosystemic shunts lead to diversion of blood from the splanchnic circulation, so that toxic metabolites including ammonia, reach the systemic circulation. Therefore, portosystemic shunts lead to a sustained increase in ammonia.[23,24] Given the fact that the presence of

TABLE 3 Multivariate logistic regression analysis to identify independent predictors of covert HE at baseline

Variables introduced			Final model			
	OR	95% CI		OR	95% CI	*P*-value
MELD	1.10	1.00-1.21	MELD	1.11	1.01-1.21	.03
Presence SPSS	3.34	0.99-11.27	Presence SPSS	3.95	1.22-12.80	.02
Prior HE	1.79	0.47-6.90				
Prior SBP	3.32	0.56-19.81				
Variables introduced			**Final model**			
	OR	**95% CI**		**OR**	**95% CI**	***P*-value**
MELD	1.10	1.10-1.00	MELD	1.11	1.01.-1.21	.026
TSA	1.01	1.00-1.02	TSA	1.01	1.00-1.02	.046
Prior SBP	2.84	0.39-20.58	Prior SBP	4.2	0.70-25.12	.007
Prior HE	1.83	0.47-7.18				

Abbreviations: CI, confidence interval; HE, hepatic encephalopathy; OR, odds ratio; SBP, spontaneous bacterial peritonitis; SPSS, spontaneous portosystemic shunt; TSA, total cross, sectional SPSS area.

TABLE 4 Incidence of complications during follow-up in all patients and comparison with logistic regression between the subgroups with No HE and covert HE

Event	Total	No HE	covert HE	*P*-value	OR (95% CI)
HE	24/65 (37%)	5/33 (15%)	19/32 (59%)	**.001**	**8.19 (2.50-26.76)**
Ascites	52/64 (81%)	26/32 (81%)	26/32 (81%)	1.00	1.00 (0.29-3.51)
GI haemorrhage	17/64 (27%)	6/33 (18%)	11/31 (36%)	.123	2.48 (0.78-7.82)
SBP	7/61 (12%)	1/32 (3%)	6/29 (21%)	.061	8.09 (0.91-71.87)
HRS	9/58 (16%)	3/29 (10%)	6/29 (21%)	.285	2.26 (0.51-10.08)
HCC	7/62 (11%)	4/33 (12%)	3/29 (10%)	.826	0.84 (0.17-4.09)
Infection	25/62 (40%)	11/33 (33%)	14/29 (48%)	.234	1.87 (0.67-5.21)
Transplant-free survival	32/65 (49%)	15/33 (46%)	17/32 (53%)	.537	1.36 (0.51-3.61)

Note: Significant p-values and CI are displayed in bold.

Abbreviations: CI, confidence interval; GI, gastrointestinal; HCC, hepatocellular carcinoma; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; OR, odds ratio; SBP, spontaneous bacterial peritonitis.

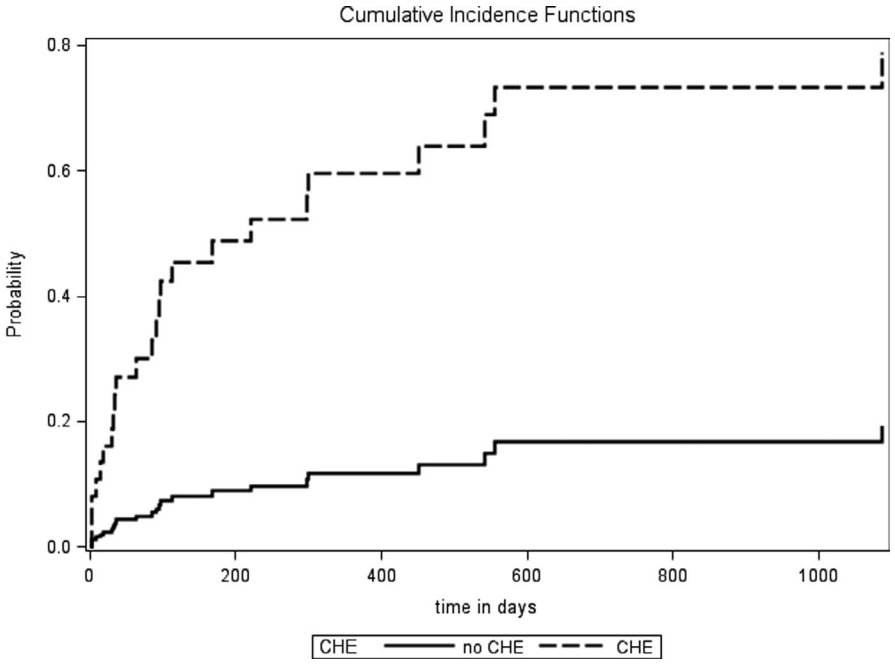

FIGURE 2 Cumulative incidence curve for development of overt HE during follow-up according to the presence of CHE. CHE-covert hepatic encephalopathy, OHE-overt hepatic encephalopathy

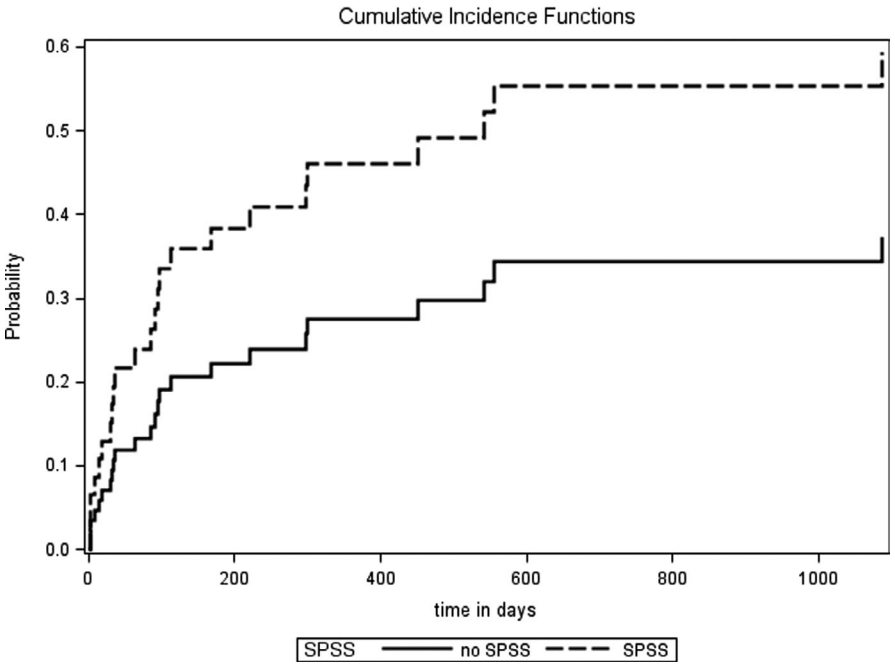

FIGURE 3 Cumulative incidence curve for the development of overt HE during follow-up according to the presence of SPSS. OHE-overt hepatic encephalopathy, SPSS-spontaneous portosystemic shunt

spontaneous portosystemic shunts are structural changes which are not modified easily, one can hypothesize that their main effect on cognitive function in cirrhosis would be sustained in nature, like covert hepatic encephalopathy. Indeed, in the present study, we observed that the mere presence of shunts, independent from their size, was associated to cHE. On multivariate analysis, both MELD score and presence of shunts were independent predictors of cHE, which reflect two of the patho-physiological mechanisms (liver insufficiency and portal hypertension by means of shunts) involved in hyperammonemia in cirrhosis.

Interestingly, in the present study, no association between the presence of SPSS and development of oHE during follow-up was observed. Among the patients who had SPSS without cHE at baseline, none developed oHE during follow-up. On the other hand, SPSS seems to modulate the risk of oHE of patients with cHE. Indeed, although patients with cHE without SPSS had a five-fold rate of oHE during follow-up, patients with cHE and SPSS had an almost ninefold increase in the rate of oHE compared to those without cHE.

This finding may seem contradictory to the previous study which demonstrated that patients with portosystemic shunts have an increased risk of oHE during follow-up.[15-17] Although this may be to the result of lack of power of the present study,

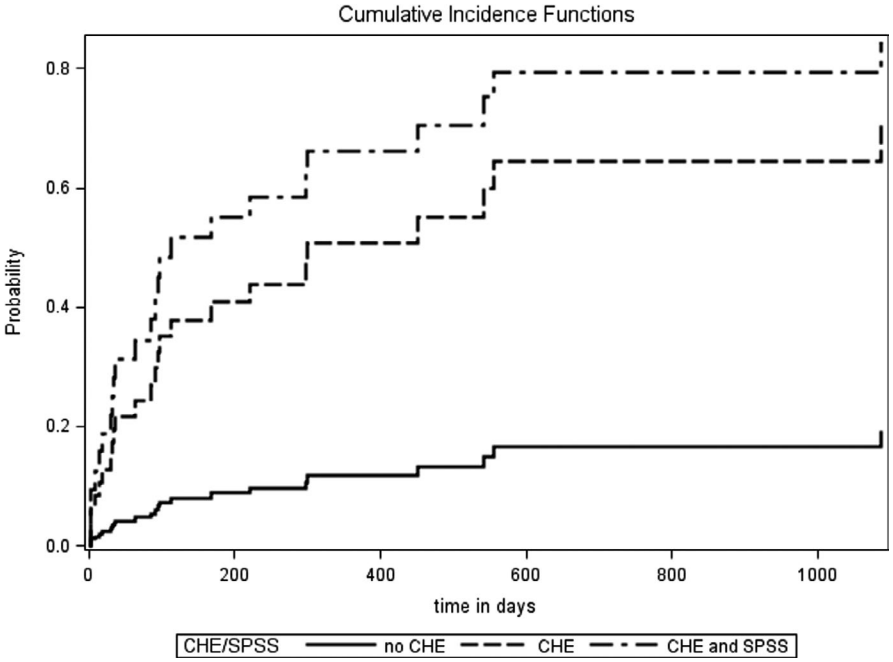

FIGURE 4 Cumulative incidence curve for development of overt HE during follow-up according to the presence of CHE with and without SPSS. CHE-covert hepatic encephalopathy, OHE-overt hepatic encephalopathy, SPSS-spontaneous portosystemic shunt

it is possible that the previously described association between SPSS and oHE during follow-up, is mediated by the association between SPSS and cHE at baseline. In this case, SPSS would favour cHE which in turn would lead to a greater risk of oHE during follow-up.

Besides the influence of SPSS on the presence of cHE at baseline, it seems that the presence of SPSS modulates the risk of oHE during follow-up in patients with cHE. Interestingly, we observed that the risk of oHE was greater in those patients with SPSS and cHE than those with cHE alone. The possible modifying effect may be owing to the combination of several factors which are associated with the development of oHE. SPSS typically lead to an increase in blood ammonia.[23,24] Chronic hyperammonaemia can lead to an increase in brain barrier permeability which could lead to an increased susceptibility to other toxins.[25] Indeed, patients with MHE do not have higher levels of ammonia than patients without MHE but rather have higher levels of markers of inflammation.[26,27] Whether the presence of both factors (cHE and SPSS) identifies patients who have more than one pathogenetic factor and therefore a higher susceptibility of oHE remains a matter of speculation.

An interesting secondary result of the study is that CFF is not associated with presence of SPSS at baseline nor does cHE as defined by CFF predict negative outcomes during follow-up. This finding further fires the debate regarding the use of CFF for the diagnosis of cHE. While some studies have shown its prognostic value in predicting oHE,[28,29] mortality[30] and its superiority to PHES in predicting post-TIPS HE,[29] others have not confirmed these results. Although there is a known correlation between plasma ammonia and CFF,[31] the CFF-results surprisingly played no role in this study investigating the association of SPSS.

Our study has several limitations inherent to its retrospective design. Firstly, no measurements of ammonia or other inflammation markers at the time of the cHE testing were available so that a mechanistic explanation cannot be provided. Furthermore, because of its retrospective design, only a small proportion (5%) of the original study sample (n = 1729) had information regarding cHE-testing available, so that despite the very large original study, the present study is considerably smaller. Furthermore, the smaller sample size precludes further analysis regarding the interaction and/or confusion between SPSS and cHE. A potential confounder for comparison of subgroups in oHE-development is the treatment with disaccharides. Indeed, there were patients on disaccharides without prior HE. This reflects the treatment reality in many parts of Germany, where disaccharides are commonly administered in cirrhosis despite lack of previous hepatic encephalopathy. Although identification of predictors of oHE was not directly the aim of the study, patients on disaccharides had an increased risk of oHE during follow-up on univariate analysis, however, their administration was not independently associated to development of oHE on multivariate analysis. Another limitation of our study is that patients with a compensated state of cirrhosis are underrepresented in the study population. In fact, the study population of the present study is sicker than the study population of the original study (see Table S1). The majority of patients presented with an advanced degree of cirrhosis (median MELD 15; 75% at least Child-Pugh class B). Since both cHE and SPSS are more frequent in patients with advanced liver disease, the results cannot be extrapolated to patients with less severe disease including compensated cirrhosis. Finally, the study population is composed of mainly patients with alcoholic disease, whether the results can be extrapolated to other aetiologies of cirrhosis is not clear.

In conclusion, cHE is independently associated to the presence of SPSS (and TSA) and MELD score. Furthermore, cHE and the

presence of SPSS have a synergistic effect increasing the risk of developing oHE during follow-up.

ETHICAL APPROVAL STATEMENT

Institutional review board approval for the present study was obtained. (Ethics committee University of Halle: 2016-36).

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

CL, AZ, CR, MST, KH, FS collected the data. CR, AZ, JG, JT planned the study and supervised the data collection. AW, CR and RG did the analysis. RG and CR wrote the paper. All authors have provided important intellectual input. All authors have approved the final draft of the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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