

# Validation of a Simple Quality-of-Life Score for Identification of Minimal and Prediction of Overt Hepatic Encephalopathy

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Minimal hepatic encephalopathy (MHE) is underdiagnosed because most clinics refrain from psychometric testing. Diagnostic activities need to go up so patients with MHE can get the treatment their condition requires. The sickness impact profile questionnaire for covert hepatic encephalopathy (SIPCHE) score is based on quality-of-life outcomes and has been proposed as a simple, patient-administered diagnostic score for grade 1 and MHE. Validate the SIPCHE for MHE identification and overt hepatic encephalopathy (OHE) prediction. 110 patients with liver cirrhosis (age 60 years, Model for End-Stage Liver Disease score of 11.4, 80% blue-collar) provided information for SIPCHE scoring: gender, age, and four SIP statements: “I do not maintain balance (physically),” “I act irritable or impatient with myself,” “I am not doing any of the usual physical recreation or activities,” and “I am eating much less than usual.” MHE was diagnosed using an abnormal continuous reaction time test and/or portosystemic encephalopathy syndrome test score. Patients were followed for 2.7 years on average. SIPCHE score positivity had high sensitivity (82%) but low specificity (38%) for MHE detection. Patients with an abnormal SIPCHE had a higher incidence of OHE during follow-up (35% vs. 14%,  $P = 0.05$ ). OHE prediction sensitivity was 87% and exclusion sensitivity was 85%. The patients with an abnormal SIPCHE had twice as many subsequent episodes of OHE, and despite their high mortality, also a higher risk. An abnormal SIPCHE had a high sensitivity and low specificity for MHE identification. An abnormal SIPCHE was associated with a more than doubled risk of OHE, even with death as a competing event. SIPCHE could be used as a high-sensitivity, low-cost, surrogate marker of MHE in clinics without availability of psychometric tests and allow more patients to benefit from anti-MHE treatment. (*Hepatology Communications* 2020;4:1353-1361).

Currently, most patients with liver cirrhosis are not examined for the presence of minimal hepatic encephalopathy (MHE).<sup>(1-4)</sup> This situation calls for attention, because despite the condition's absence of clinical symptoms, MHE severely impinges on the patient's quality of life (QoL) and increases the of falls, traffic accidents, and later development of overt hepatic encephalopathy (OHE).<sup>(5-10)</sup> Furthermore,

*Abbreviations: CHE, covert hepatic encephalopathy; CI, confidence interval; HE, hepatic encephalopathy; MELD, Model for End-Stage Liver Disease; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; PHEs, portosystemic hepatic encephalopathy score; PRO, patient-related outcome; PSE, portosystemic encephalopathy; QoL, quality of life; sHR, subdistribution hazard ratio; SIP, sickness impact profile questionnaire.*

*Received February 29, 2020; accepted May 17, 2020.*

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*DOI 10.1002/hep4.1555*

*Potential conflict of interest: Dr. Bajaj is on the speakers' bureau for Norgine. Dr. Munk Lauridsen advises Umecrine Cognition. She is on the speakers' bureau for Norgine.*

MHE is effectively treatable: A 2016 Cochrane meta-analysis concludes that lactulose improves MHE with a very low number needed to treat of 4, and prevents future episodes of OHE with a number needed to treat of 7.<sup>(11)</sup>

MHE diagnostic activities need to go up, because too many patients with cirrhosis do not get the treatment their condition requires. Psychometric and neurophysiological testing remain the established standard for the diagnosis of MHE; however, simple, sensitive, self-administered screening tests might encourage clinicians to test and treat MHE in a larger scale. Patient-reported outcomes (PROs) such as QoL indices are under study for their usefulness in diagnosis of grad 1 HE and MHE, detection of anti-HE treatment effects, and for OHE prediction.<sup>(12,13)</sup> This approach is particularly relevant in MHE, because many of the patients' problems are related to QoL reductions, which appear to improve with treatment.<sup>(14-17)</sup> Thus, patient-administered QoL questionnaires, such as the generic and standardized sickness impact profile (SIP), could prove useful in identifying patients with MHE and improving the treatment coverage.

The SIP questionnaire is easy to understand and to complete but is comprehensive, takes a long time to complete, and requires a sustained level of attention. For patients with MHE and wavering attention, a simplified version is necessary. The use of a simplified SIP as both a measure of QoL and as a tool to identify MHE was recently evaluated in a US-based study.<sup>(18)</sup> They used a SIP-based score that was tailored and simplified to find covert hepatic encephalopathy (CHE i.e. grade 1 and MHE) and therefore named the SIPCHE score. This score consists of

only four selected SIP statements, gender, and age. It was able to identify more than 80% of psychometry-diagnosed patients with MHE in the founding cohort. However, before further applying the SIPCHE score, validation of it in an external cohort with a potentially different case mix and perceived illness burden is needed.<sup>(18)</sup>

The aim of our study was to validate the SIPCHE score for MHE identification in a Danish cirrhosis cohort, using the continuous reaction time (CRT) test and the portosystemic hepatic encephalopathy score (PHES) for MHE diagnosis. The patients were followed for episodes of OHE, and the prediction by SIPCHE was calculated.

## Patients and Methods

### PATIENTS

We included patients with liver cirrhosis diagnosed by liver biopsy or unequivocal clinical and biochemical findings. All completed the SIP and had a CRT and portosystemic encephalopathy (PSE) test at the same occasion. Participants were all found to be mentally unimpaired and acquitted of OHE (West Haven grade 1-4) by an experienced hepatologist. We excluded patients with severe hyponatremia (plasma sodium < 125 mmol/L), renal failure (creatinine >1.7 g/dL), dementia (Mini-Mental State Examination score <24), ongoing alcohol use, recent sepsis or bleeding (7 days), use of opioids, myxedema, and ongoing HE treatment (Fig. 1). The stable use of antidepressant was allowed.

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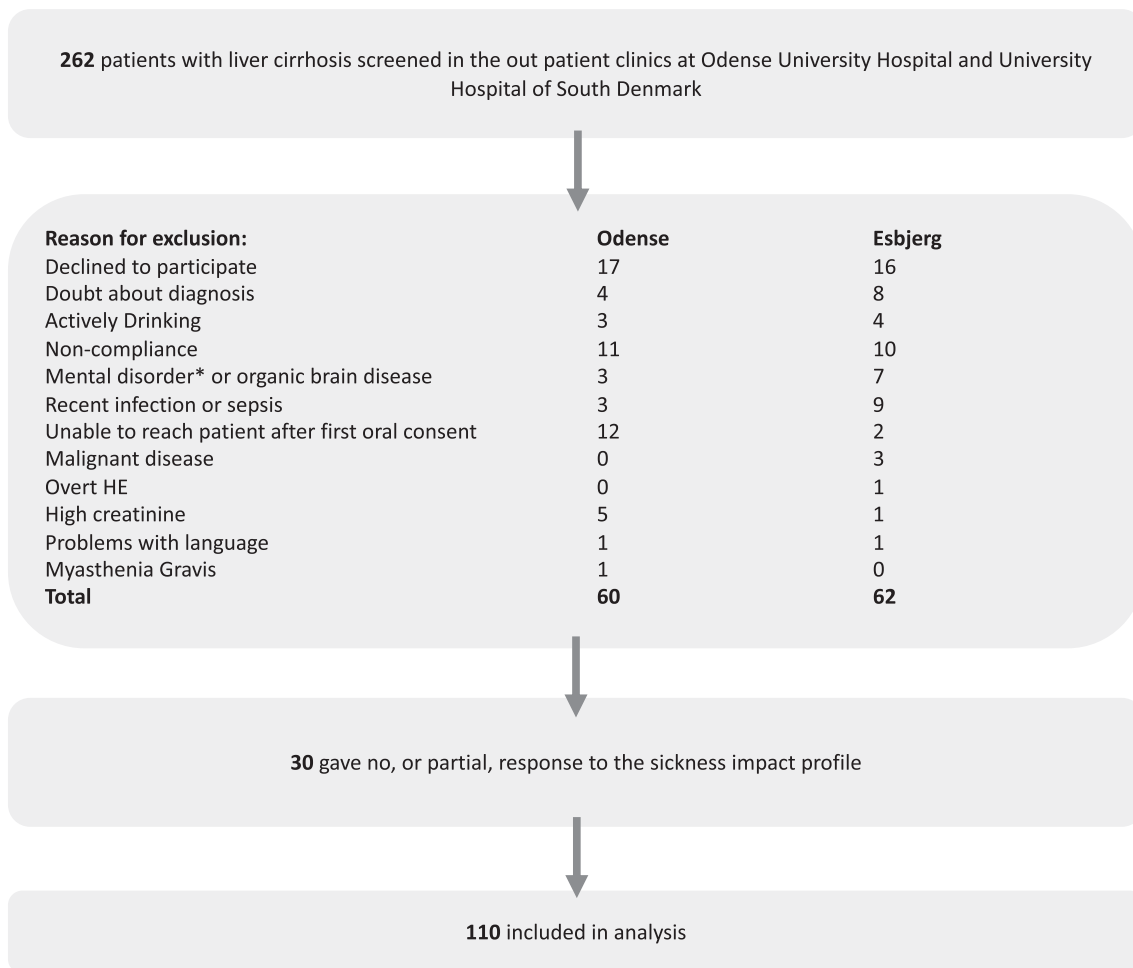


FIG. 1. Participant screening process.

The participants were recruited for a cross-sectional study aiming to compare the CRT and PSE tests. A subgroup continued into a 3-month anti-MHE treatment RCT immediately after the tests, and only 6 patients received multimodal anti-HE treatment.<sup>(19,20)</sup> The study protocol adhered to the 1975 Helsinki Declaration and was approved by the Danish National Committee on Health Research Ethics. Participants gave their informed written consent prior to participation, and the follow-up data presented here were reported to, and approved by, the regional data protection office according to Danish law.

## DEFINITION OF OHE EVENTS

OHE does not have a unique International Classification of Diseases code. OHE events were

sought manually from each of the electronic patient files by a single observer (C.W.W.). The files hold complete information for all Danish hospitals. We sought out doctors' and nurses' notes at all hospital admissions. We recorded any mention of the patient having HE as an HE event.

## ANTI-HE TREATMENT DURING FOLLOW-UP TIME

The psychometric testing did not influence the clinical decisions toward anti-HE treatment, as the methods were not validated in 2013 for that purpose in Denmark. Episodes of OHE were treated with lactulose, and rifaximin was added as secondary prophylaxis against recurrent OHE. The adherence to lactulose after discharge from hospital cannot

be documented, since lactulose is also an over-the-counter drug.

## SIPCHE

The SIPCHE was introduced as a diagnostic tool for CHE in a US cohort of 170 patients with liver cirrhosis,<sup>(18)</sup> in whom CHE diagnosis was given by impairment in two or more of the following psychometric tests: the number connection test A and B, the digit symbol test, and the block design test. The SIPCHE score is based on significant answers for CHE diagnosis, selected through regression analyses. The following SIP statements were included: “I do not maintain balance,” “I act irritable or impatient with myself,” “I am not doing any of the usual physical recreation or activities,” and “I am eating much less than usual.” The SIPCHE score was therefore calculated from the following formula:

$$\text{SIPCHE} = -0.6 + 0.1 * \text{Age} + 0.9 * \text{male gender} + 2.6 * \text{BCM4} + 2.4 * \text{EB7} + 1.9 * \text{RP8} + 1.9 * \text{E1}$$

## CRT TEST

The CRT test is a 10-minute computerized test (Ekho software; Bitmatic.com, Aarhus, Denmark) assessing the patient’s alertness, psychomotor speed, and response inhibition.<sup>(21)</sup> A body of evidence support its utility as a diagnostic test for MHE.<sup>(19,21-24)</sup> Before the test, the patient is equipped with headphones and a trigger button in the dominant hand, both of which are linked to a laptop computer. During the test the computer software generates 150 sound stimuli occurring with random intervals of 2-6 seconds. The patient’s task is to respond as quickly as possible to the stimuli by pressing the trigger button. The main result of the CRT—the CRTindex (50th percentile/90th-10th percentile of all reactions)—is given by the software and is a measure of reaction time variability. When the CRT index is below 1.9 (high reaction time variability), it is indicative of MHE. The CRT index is not influenced by age, gender or educational level, shows no learning effect, and has good retest reliability.<sup>(19,21-26)</sup> We administered the test at the same time as the PSE test, in an undisturbed room in the outpatient clinic. After introducing the test, we left the patient alone in the room (doors closed; mobile phones turned off) for the time it took to complete it.

## PSE SYNDROME TEST

The PSE is a paper-and-pencil test battery that gives a measure of complex cognitive functions such as attention, accuracy, working speed, and visual orientation.<sup>(27,28)</sup> The PSE consists of five subtests (digit-symbol test, number connection test A, number connection test B, serial dotting test, and line tracing test) and takes 10-15 minutes for the patient to complete and 5 minutes for the staff to score. For each subtest, age-adjusted and region-specific normal values are available. If the time spent (seconds) on a test is within the range of -1 to 1 SD from the norm, then a score of zero is given. The subtest scores range from -3 to 1. The line tracing test is evaluated by two scores: a time score and an error score. Accordingly, in the summed test score, the PHES ranges from -18 to 6, and a result below -4 is abnormal and indicative of MHE. The PSE test was endorsed by the European Association for the Study of the Liver/American Association for the Study of Liver Diseases as a common comparator test, because it is well-validated for diagnosing and grading MHE and is used widely.<sup>(27,28)</sup> All participants were guided throughout the PSE test procedure by a single operator in an undisturbed room (doors closed; mobile phones turned off) in the outpatient clinic.

## MHE DIAGNOSIS

MHE was diagnosed by either one or both of the CRT and PHES tests showing an abnormal result. Our previous studies indicated that a patient with any single one of the tests being abnormal has an increased risk of future OHE.<sup>(19,29)</sup> The psychometric data from all participants in the presented analysis have been reported previously, but the cohort presented here is smaller because we only obtained complete SIP answers from 110 of 140 patients.<sup>(19,29)</sup> The SIP and SIPCHE data and their comparisons with the psychometry data and later OHE occurrence have not been reported.

## STATISTICAL METHODS

We classified the patient as having MHE if the CRT test or the PSE test was abnormal. The SIPCHE was taken to be abnormal when equal to or above zero. For the follow-up data we computed the incidence of episodes of OHE for those with a



normal and abnormal entry SIPCHE score. The high mortality of patients with cirrhosis may influence the risk for experiencing OHE. To this end we used a competing risks model (syntax: `stcrreg`).<sup>(30,31)</sup> This takes into account that patients may die without experiencing OHE and death is therefore a competing event. Only two transplants were done and ignored in our analysis. The competing risk analysis gives a sub-distribution hazard ratio (sHR), which indicates if the cumulative risk of OHE is higher for patients with an abnormal SIPCHE score.

## Results

### PARTICIPANT CHARACTERISTICS

We consecutively screened 262 patients in a stable disease state for eligibility, in the hepatology outpatient clinics at Odense University Hospital and the University Hospital of South Denmark from November 2013 to December 2014. We found 140 to be eligible (Fig. 1). All were diagnosed with liver cirrhosis by liver biopsy (45%) or unequivocal clinical and biochemical findings. We obtained a complete SIP response from 110 of 140 (78%) patients, and these were included in the analysis presented here. Termination of the follow-up period was May 2017. Baseline characteristics and main results are summarized in Table 1. The mean age of participants was 60 years (range 40-79), and two-thirds were male. Patients were educated for an average of 10.7 years (range 4-18), 80% had blue-collar professions, and 80% were on sick leave or were unemployed. Cirrhosis etiology was alcohol in 90%, and the median Child-Pugh Score was 6.9 (range 5-13, 53% class A, 38% class B, 9% class C). The mean Model for End-Stage Liver Disease (MELD) score was 11.4 (95% confidence interval [CI] 10.6-12.2). Previous episodes of OHE had occurred in 27% (30 of 110).

### SIPCHE FOR MHE IDENTIFICATION

Sixty-four percent (71 of 110) of the patients had MHE as diagnosed by CRT index below 1.9 and/or PHES below -4. The SIPCHE was in accordance with psychometry in 66% (73 of 110) of cases. The SIPCHE score was abnormal in 82% (58 of 71) with MHE according to psychometry (positive predictive

**TABLE 1. CHARACTERISTICS OF 110 PARTICIPANTS WITH LIVER CIRRHOSIS AND AVAILABLE DATA FOR SIPCHE CALCULATION**

	No MHE (n = 39)	MHE (n = 71)	P
Mean age (SD, range)	59.3 (7.6, 44-76)	59.7 (9.2, 40-79)	0.80
Male (%)	26 (74)	48 (68)	1.00
Blue collar (%)	28 (72)	62 (87)	0.07
Education (SD, range)	11.18 (2.6, 4-16)	10.56 (2.2, 7-18)	0.20
Charlson comorbidity score (SD, 95% CI)	3.4 (1.03, 3.1-3.7)	3.5 (1.2, 3.2-3.8)	0.94
Previous HE episodes (%)	7 (18)	23 (32)	0.12
Plasma sodium (SEM)	137.8 (0.56)	134.5 (1.32)	0.07
Child-Pugh (SD, 95% CI)	6.3 (1.7, 5.8-6.9)	7.2 (1.8, 6.8-7.7)	0.01
MELD (SD, 95% CI)	10.7 (3.8, 9.4-11.9)	11.8 (4.4, 10.7-12.9)	0.17
CRT index (SD, 95% CI)	2.5 (0.08, 2.3-2.6)	1.5 (0.05, 1.4-1.6)	<0.0001
PHES (SD, 95% CI)	-0.6 (2.29, -1.41-0.08)	-5.5 (4.4, -6.51-4.42)	<0.0001
Abnormal SIPCHE (%)	24 (50)	58 (89)	0.02
Months in the study (SD, 95% CI)	34.1 (13.2, 29.8-38.45)	29.7 (17.0, 25.7-33.7)	0.16

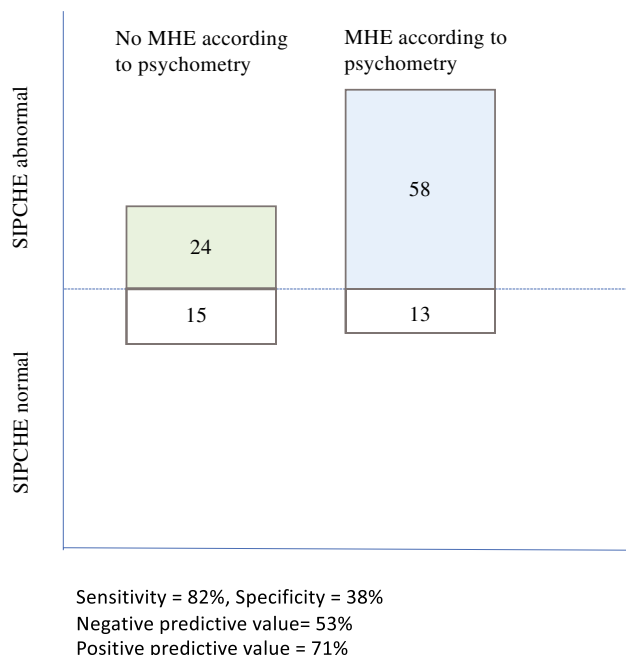
Note: MHE was diagnosed by abnormal result in CRT and/or PSE score.

value = 71%, sensitivity = 82%) and in 62% (24 of 39) with no MHE (negative predictive value NPV = 53%, specificity 38%) (Fig. 2). This means that the SIPCHE identified 82% of the patients with MHE but overlooked 18% (13 of 28).

### SIPCHE FOR OHE PREDICTION

We followed the cohort for a mean of 2.6 years (total at-risk time = 283 years). During the follow-up, 30% (33 of 110) experienced an OHE event (Fig. 3) and 44% (48 of 110) died, 27% (30 of 110) without experiencing OHE. The group with normal SIPCHE had a longer observation period (36 months, 95% CI 31-41 months) than those with abnormal SIPCHE (29 months, 95% CI 26-33 months,  $P = 0.05$ ). We found that 14% (4 of 28) with a normal SIPCHE later experienced OHE, and 36% (10 of 28) died, 25% (7 of 28) without any OHE event. Among those with an abnormal SIPCHE, 35% (29 of 82) later experienced OHE ( $P = 0.05$ ) (Figs. 2 and 3), and 46% (38 of 82) died, 28% (23 of 82) without an OHE event. The SIPCHE prediction sensitivity for future OHE was 87% (29 of 33, likelihood ratio 2.4, 95% CI 0.8-6.2,  $P = 0.11$ ).

Patients with an abnormal SIPCHE score had a higher cumulative risk of OHE (sHR 2.2, 95% CI



**FIG. 2.** The accordance between minimal hepatic encephalopathy (MHE) diagnosed by abnormal psychometry (CRT and/or PHES) and the SIPCHE score in 110 patients with liver cirrhosis.

0.8–6.2) with death as a competing event (Fig. 4). The same was true for patients with MHE as diagnosed by abnormal CRT and/or PSE (sHR 1.3, 95% CI 0.5–2.5).

We observed a well-known increase in OHE incidence with increasing liver disease severity: 70% in class C, 40% in class B, and 14% in class A experienced OHE during follow-up. Importantly, even after controlling for Child-Pugh Class, SIPCHE was predictive of OHE risk (adjusted sHR = 2.43, 95% CI 0.82–7.20).

The cumulative risk of death without OHE was not significantly higher in patients with abnormal SIPCHE (sHR 1.0, 95% CI 0.5–2.5). In patients with MHE, as diagnosed by abnormal CRT and/or PSE, the risk cumulative of death was higher (sHR 1.3, 95% CI 0.6–2.8).

## Discussion

### SIPCHE FOR MHE IDENTIFICATION

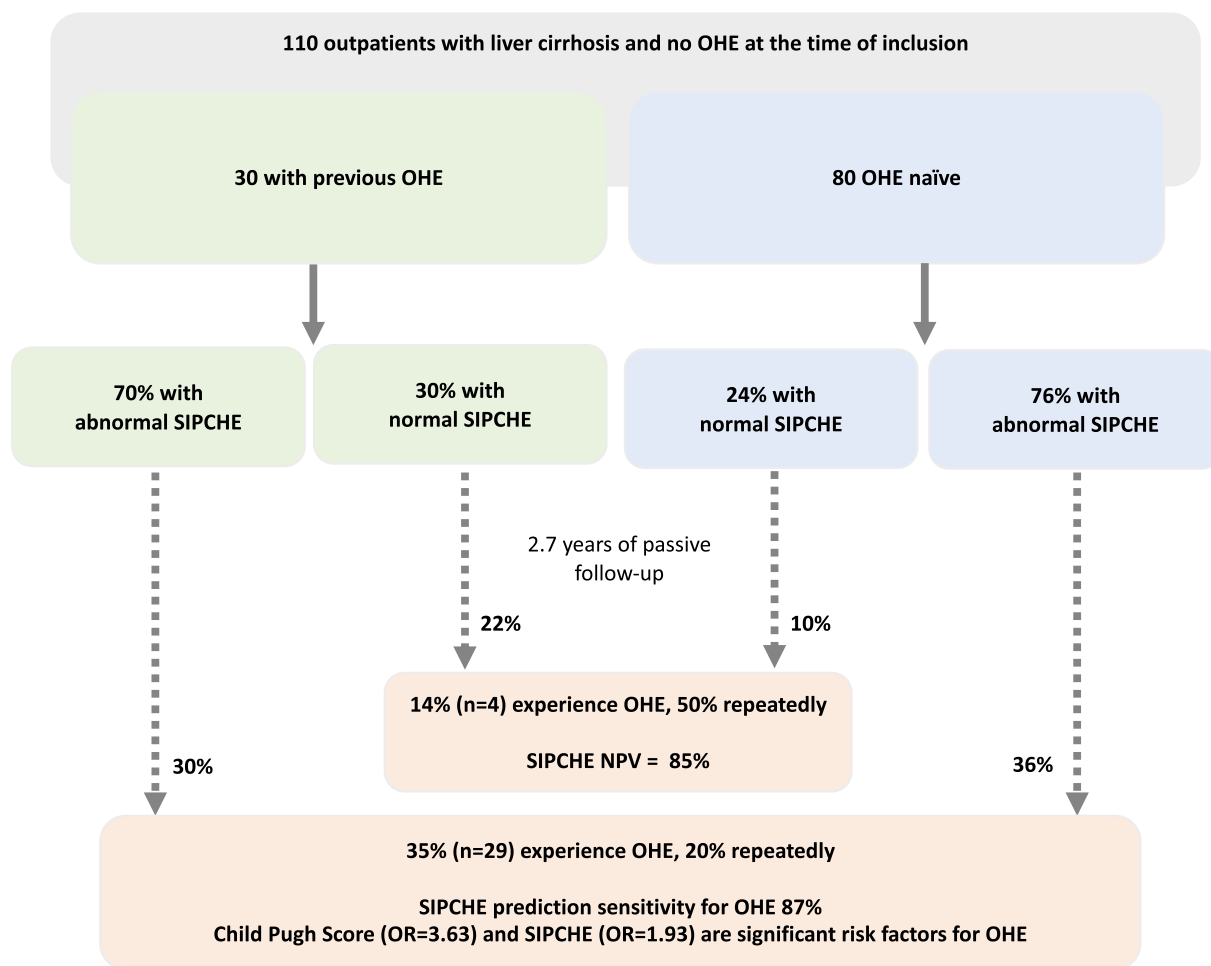
In our psychometry-tested cohort, the SIPCHE identified two-thirds of the MHE cases and had a diagnostic sensitivity of 82% and specificity of 38%.

This is similar to what was observed in the US development cohort, even though our cohort consisted of patients with MHE (not grade 1 HE), was older, had a higher proportion of alcoholic cirrhosis and slightly more severe liver disease (approximate MELD = 8 vs. 12).<sup>(18)</sup>

An important issue is whether, and how, the SIPCHE should be applied in relation to psychometric testing. The strength of the SIPCHE is that it is fast, and therefore possible for the patients to complete in the waiting room or at home, and adds the patients' perspective into MHE identification. The inherent limitations of the score is that it does not give a measure of brain functioning, as the psychometric tests do. Furthermore, QoL, and as such the SIPCHE, is affected by numerous factors not linked to MHE-associated brain dysfunction. Another important issue is that we do not know the magnitude of random variation for SIPCHE, nor its ability to detect a response to anti-HE treatment, whereas this is well-characterized for at least the CRT test. Nonetheless, our data support the notion that in clinics not using psychometric tests at all, SIPCHE could be used by itself as a basis for initiating anti-HE treatment. This approach, while not being rooted in the patients' brain function, may still be justifiable by the fact that anti-HE treatment by lactulose is cheap and safe, and the consequences of treating false positives are therefore negligible—an acceptable risk profile as compared with the risk of treating too few and facing the serious event of OHE and hospital admission.

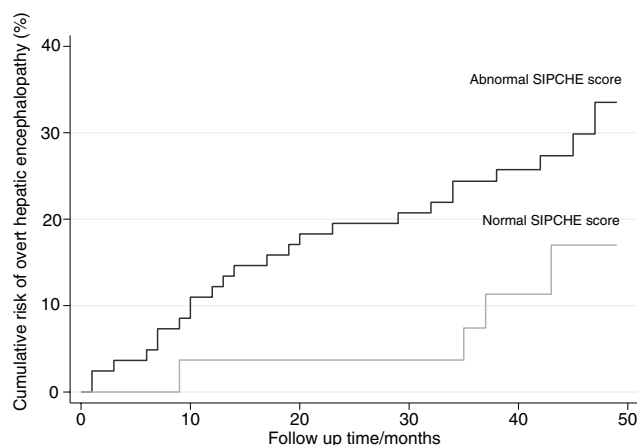
### SIPCHE FOR OHE PREDICTION

Our study extends previous studies by incorporating almost 3 years of complete cohort follow-up, making it possible to look for the effect of an abnormal SIPCHE on the incidence and risk of subsequent OHE episodes. This is important for the validation of the score, because one of the major advantages of identifying MHE is that the condition increases the incidence of subsequent bouts of OHE, which can be reduced by preventive lactulose treatment.<sup>(29,32)</sup> We found that 35% of our patients with an abnormal SIPCHE score later experienced one or more OHE episodes versus 14% in the group with a normal SIPCHE. SIPCHE had a prediction sensitivity for subsequent OHE of 87% and a good ability to exclude future OHE (i.e., a negative predictive value of 85%). Because of the high mortality



**FIG. 3.** The participants' flow through the study according to prior HE status. Abbreviations: NPV, negative predictive value; OHE, overt hepatic encephalopathy; OP, odds ratio.

rate of cirrhosis and the difference in observation time between the SIPCHE groups, however, it remains uncertain what the *risk* was for the patients with an abnormal SIPCHE to actually experience their first OHE episode while under study. We therefore expanded the analyses to take into account the cohort mortality in a competing risks model. This analysis confirmed that the patients with an abnormal SIPCHE had a more than doubled OHE risk (as reflected by the sHR of 2.24, notwithstanding the wide confidence interval). The observation remained true even within each Child-Pugh class. This is important knowledge to the clinician: SIPCHE is not only associated with a higher OHE incidence, but the actual risk is increased so that the need for prevention remains relevant despite the patients' high mortality. This risk analysis is likely



**FIG. 4.** The observed cumulative risk of OHE in 110 patients with liver cirrhosis and normal (gray line) and abnormal (black line) SIPCHE score.

even conservative, because it does not take into account recurrent episodes.

We know from our previous studies that psychometry-based MHE (CRT and/or PSE abnormal = MHE) has a prediction sensitivity for OHE of 77%, a negative predictive value of 81%, and identifies the group of patients with the highest subsequent OHE admission rate.<sup>(20,29)</sup> Thus, SIPCHE in this cohort had a predictive value for OHE comparable to that of psychometry despite the generic character of QoL scores. Furthermore, prediction analysis has the limitation that the terms for clinical decision may have changed toward a proactive test-and-treat approach during the follow-up time after publication of psychometric test validation studies. This might have reduced the OHE occurrence rate toward the end of the follow-up period and thus weakened our prediction estimates, implying that we might have had better prediction by SIPCHE without this possible bias, which would be the same for the whole cohort.

Our observations are backed by others who have found a similar degree of parallelism between the brain function and QoL measures in liver disease. Studies by Patidar et al. and Labenz et al. showed that PROs could predict outcomes in cirrhosis.<sup>(12,33)</sup> Collectively, these findings indicate that it may be time to consider PROs in the evaluation of patients with cirrhosis.<sup>(34)</sup>

In conclusion, the simple PRO score, the SIPCHE, was promising as a substitute for psychometry for the identification of MHE in patients with cirrhosis. The SIPCHE also to a degree identified patients at higher risk of experiencing subsequent OHE, even taking into account such patients' high mortality. Future studies should describe the random variation of SIPCHE and its ability to document a treatment response. The latter is of special interest in contributing to the patient-experienced effect of HE treatment.

*Acknowledgment:* The authors thank Dr. Heuman for his role as a co-developer of the SIPCHE score.

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