Multimodal assessment of covert hepatic encephalopathy and its outcome in a prospective cohort of outpatients with chronic liver disease

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BACKGROUND/AIM

Covert hepatic encephalopathy (CHE) is difficult to diagnose in patients with chronic liver disease (CLD), as other aetiologies may cause neurocognitive impairment. The aim of this study was to phenotype outpatients with CLD with a suspicion of covert hepatic encephalopathy, and to assess further development of overt hepatic encephalopathy (OHE), liver-related rehospitalization (LRH) and liver transplantation free-survival during follow-up.

PATIENTS & METHODS

Retrospective analysis of a prospective cohort of patients with CLD (from March 2018 to November 2022) referred to our outpatient clinics for suspicion of covert hepatic encephalopathy. Exclusion criterion was previous LT. Multimodal work-up was performed including clinical examination, psychometric tests, biomarkers including ammonia, EEG, brain MRI with spectroscopy. Triphasic peaks on EEG, increase of N-acetyl aspartate and Glutamate/Glutamine with decrease of Myoinositol and Choline at spectroscopy suggested CHE.

Patients were followed for development of overt hepatic encephalopathy, liver-related hospitalizations occurrence, liver transplantation-free survival and overall survival. Analyses were performed with survival model.

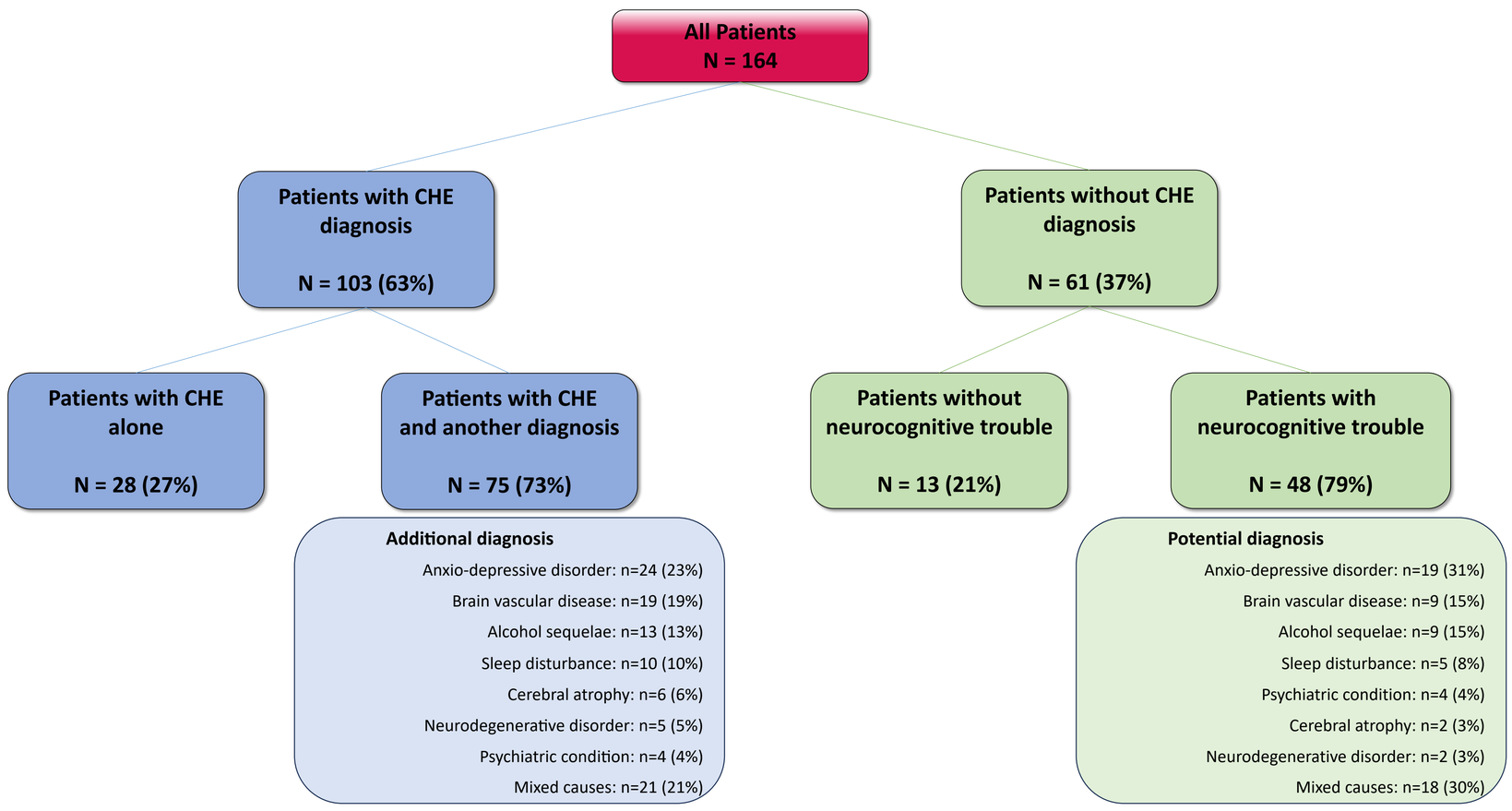
RESULTS

Baseline characteristics of the patients

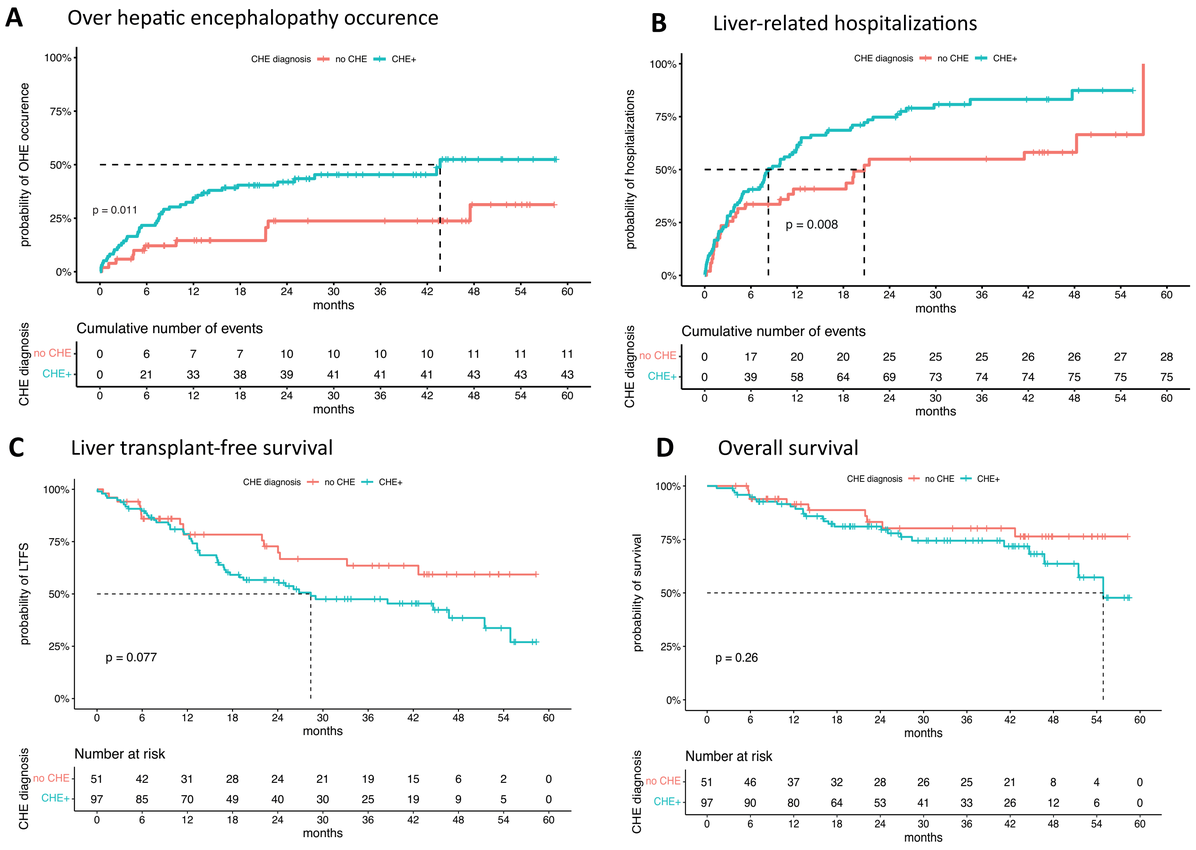
	Overall N=164	Patients without covert hepatic encephalopathy n=61 (37%)	Patients with covert hepatic encephalopathy n=103 (63%)	p-value
Men; n (%)	105 (64)	35 (57)	70 (68)	0.2
Age; year, median (IQR_1-IQR_3)	60 (50-66)	57 (47-65)	60 (52-66)	0.2
Etiology of chronic liver disease; n (%)				
Cirrhosis	127 (77)	43 (70)	84 (82)	0.1
Heavy drinking	79 (62)	28 (65)	51 (61)	0.9
MASH	68 (54)	16 (37)	52 (62)	0.002
Virus	20 (16)	7 (16)	13 (15)	>0.9
Mixed causes	49 (39)	13 (30)	36 (43)	0.2
Child-Pugh class (A/B/C)	29/78/12 (24/66/10)	18/19/4 (44/46/10)	11/59/8 (14/76/10)	0.001
MELD score; median (IQR_1-IQR_3)	12 (9-15)	10 (8-12)	13 (11-15)	<0.001
Vascular liver disease	38 (23)	16 (26)	22 (21)	0.5
Previous TIPS placement; n(%)	47 (29)	13 (21)	34 (33)	0.11
Previous episode of hepatic encephalopathy; n(%)	115 (70)	31 (51)	84 (82)	<0.001
Specific medication for hepatic encephalopathy; n (%)	113 (98)	29 (48)	84 (82)	<0.001
Comorbidities; n(%)				
Diabetes	60 (37)	17 (28)	43 (42)	0.07
Body mass index-kg/m2; median (IQR_1-IQR_3)	26.1 (23.5-30.2)	25.6 (22.1-28.6)	27 (24.1-30.7)	0.05
Obesity at time of evaluation	43 (27)	9 (16)	34 (33)	0.02
Active alcohol abuse at evaluation	14 (8)	7 (11)	7 (7)	0.3
History of brain damage				
Ischemic stroke	14 (8)	2 (3)	12 (12)	0.06
Traumatic brain injury	12 (7)	3 (5)	9 (9)	0.5
Anxio-depressive disorder	32 (20)	16 (26)	16 (16)	0.09
Psychiatric disease	9 (5)	5 (8)	4 (4)	0.3
Psychotropic drug medication	41 (25)	18 (31)	23 (23)	0.3

MASH: metabolic associated steatohepatits, MELD: Model for End-Stage Liver Disease, TIPS: transjugular intrahepatic porto-systemic shunt

Covert hepatic encephalopathy (CHE) diagnosis



Outcomes of patients with or without covert hepatic encephalopathy



- **Median follow-up time was 26 (13-44) months**
- **Patients CHE+ had significantly more OHE than patients CHE- during follow-up with a 1-year and 4-year probability at 34.6% and 52.4% vs 14.6% and 31.3%, log-rank = 0.01**
- **Patients CHE+ had more LRH than patients CHE- with a 1-year and 4-year probability at 61.6% and 87.4% vs 40.8% and 58.1%, log-rank=0.008**
- **The 1-year and 4-year probability of LTFS was 78.6% and 38.5% vs 78.4% and 59.3% in patients CHE+ and CHE- respectively, log-rank=0.08**
- **The 1-year and 4-year probability of OS were 90.4% and 63.6% vs 91.4% and 76.4% in patients CHE+ and CHE- respectively, log-rank=0.26**

CONCLUSION:

Less than 2/3 of outpatients with CLD and suspicion of CHE were finally diagnosed with CHE, and among them 3/4 also displayed another cause of NI.
Differential work-up must be performed in patients with suspicion of CHE, as a significant proportion of them present nonreversible causes of neurocognitive troubles like vascular leukopathy or alcohol sequalae.
CHE diagnosis was associated with a significantly higher rate of OHE development and LRH.