Editorial

Severe hepatic encephalopathy is an independent predictor of mortality in hospitalised patients with cirrhosis

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Hepatic encephalopathy (HE) is one of the most debilitating complications to cirrhosis (1). It has a considerable impact on patients as well as their caregivers and the health care system. The condition is defined as a brain dysfunction caused by liver insufficiency or portal systemic shunting. The symptoms, which are potentially reversible, vary from subclinical to deep coma. Symptomatic, also known as overt HE is a marker of decompensated cirrhosis. Overt HE may be precipitated by an event such as infection or bleeding, but often, no precipitating factor is identified. Overt HE is generally graded based on the severity of the symptoms according to the four-point West Haven Scale (2). The highest (worst) grade (3 to 4) are characterised by impaired consciousness. Grade 3 HE is diagnosed in patients with somnolence/semi-stupor, who remain responsive to stimuli; are confused, show gross disorientation or bizarre behaviour. Grade 4 is defined as coma (not responsive to stimuli). According to the time course, HE is defined as episodic, recurrent or persistent. In patients with cirrhosis, the risk of developing HE is closely related to the severity of the underlying liver disease (3).

Unfortunately, mortality associated with HE remains high in spite of evidence-based treatments such as rifaximin (4) as well as non-absorbable disaccharides (5).

In their epidemiological study including data from the North American consortium for study of end-stage liver disease database, Bajaj *et al.* show that severe HE is an independent predictor of mortality (6). The finding is important because it shows that the association between HE and mortality does not simply reflect increased mortality associated with worsening of the underlying liver disease.

In their study, Bajaj *et al.* included 1,560 hospitalised patients with cirrhosis. Only tertiary centres were included and all patients received the best standard of care. In total, the study includes 516 patients with HE. The grade of HE was recorded at admission and during hospitalization as well as the precipitating factors (e.g., infections, upper gastrointestinal bleeding, medications, constipation, and transjugular intrahepatic portosystemic shunt insertion). The analyses focused on the maximum grade of HE. In total, 371 had grade 1 to 2 HE. Only 9% of included patients (n=145) had grade 3 to 4 HE. Four hundred and four patients had HE on admission and 117 developed HE during hospitalization. Only 41 of the 117 patients in the latter group (3.5%) had grade 3 to 4 HE. As shown in the *Figure 1*, which is based on data from the study (6), grade 3 to 4 is associated with increased in-patient as well as 30-day mortality. Grade 1 to 2 HE does not appear to increase mortality and has a lower mortality risk than grade 3 to 4 HE. The patients with grade 3 to 4 HE also had an increased risk of complications including organ failure such as renal impairment. The increased mortality risk remained statistically significant after adjusting for other complications.

Diagnosing HE may be relatively easy, e.g., in a patient with known cirrhosis admitted with infection and impaired consciousness. In other patients, the diagnosis and grading may be difficult. The difficulties can impede the interpretation of studies evaluating HE. Bajaj *et al.* chose to compare grade 0; 1 to 2; or 3 to 4 HE. Previous evidence suggests that this

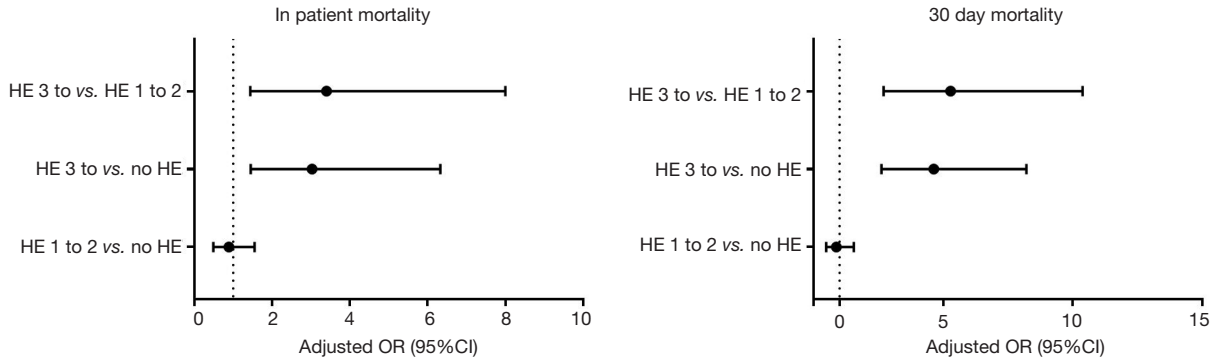

Figure 1 The figure illustrates the adjusted OR with 95% confidence intervals from adjusted analyses from an epidemiological study by Bajaj *et al.* comparing patients without HE, grade 1 to 2 HE and grade 3 to 4 HE (6). The analyses found that HE grade 3 to 4, but not grade 1 to 2 increases in-patients and 30-day mortality. OR, odds ratios; HE, hepatic encephalopathy.

strategy provides high interrater reliability (7).

The treatment of HE includes correction of precipitating factors and prevention of complications such as those associated with impaired consciousness. Bajaj *et al.* included data from experienced tertiary centres only. Theoretically, it is possible that the inclusion of data from non-specialised centres would have generated a different result. Both aspects of achieving the correct diagnosis combined with treatment strategies could influence the findings. The 30-day mortality was clearly higher than the in-patient mortality suggesting that care after discharge is important. Potential problems include non-adherence to treatment as previously shown in trials evaluating adherence to the non-absorbable disaccharide lactulose (8). Additional trials and studies may help the development of strategies to improve care and monitoring of patients in the outpatient setting.

Given the impressive data set the authors have collected it would be interesting to study outcomes over a longer follow-up period in order to evaluate whether the difference in survival between patients with no, mild or severe HE is persisting over months. Given the relative high risk of both extrahepatic organ failure, death and HE in their population it is possible that a multistate survival analysis accounting for the obvious competing risk situation could disentangle the relations between risk factors and unfavourable outcome (9).

The model for end-stage liver disease (MELD) score is used in the prioritization of patients with cirrhosis for liver transplantation (10). HE is not included in the MELD score. The results of Bajaj *et al.* suggest that HE should be considered as an important risk factor to avoid underestimating the risk of death (6). A study based on the United Network for Organ Sharing registry data, we evaluated the impact of HE on waiting-list mortality. Of 84,947 patients in the study; 37% had no HE, 57% had grade 1 to 2, and 6% had grade 3 to 4 HE. The study found that the 90-day mortality was higher for patients with grade 3 to 4 compared with patients with grade 1 to 2 or no HE (24% *vs.* 7% *vs.* 4%; P<0.001). The combination of the severity of HE and the MELD score provided the best prediction of mortality.

In conclusion, the combined evidence suggests that severe HE with impaired consciousness is an important independent risk factor in patients with cirrhosis.

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Footnote

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