

Response to reviewers

- Moderate to severe 25-OHD deficiency was identified in 49 patients of whom 36 had *grade 2-3 HE* compared with 13 patients who were not.
- The distinction between covert and overt hepatic encephalopathy has been acknowledged and hepatic encephalopathy is now called overt hepatic encephalopathy (OHE). The manuscript does not suggest that 25-OHD insufficiency or deficiency is a predictor of chronic liver disease as 25-OHD levels may be influenced by other factors such as dietary intakes and exposure to sunlight. Our findings confirm the findings of other investigators that the incidence of 25-OHD deficiency is common. Amendment to the manuscript as below:

As the first step in the hydroxylation of vitamin D occurs within the liver it is anticipated that 25-OHD levels would fall with progressive liver dysfunction. In fact, vitamin D deficiency has been reported in up to 92% of patients with chronic liver disease and at least one third of these have severe 25-OHD deficiency^[33].

- The relationship between Child-Pugh classification and 25-OHD has been clarified:

25-OHD deficiency is associated with increasing Child-Pugh classification rather disease aetiology^[34] and is more prevalent in patients with cirrhosis than those who are not cirrhotic^[33].

- 25-OHD insufficiency or deficiency is associated with overt HE but unlike elevated serum ammonia is not predictive of overt HE. Amendment to manuscript below:

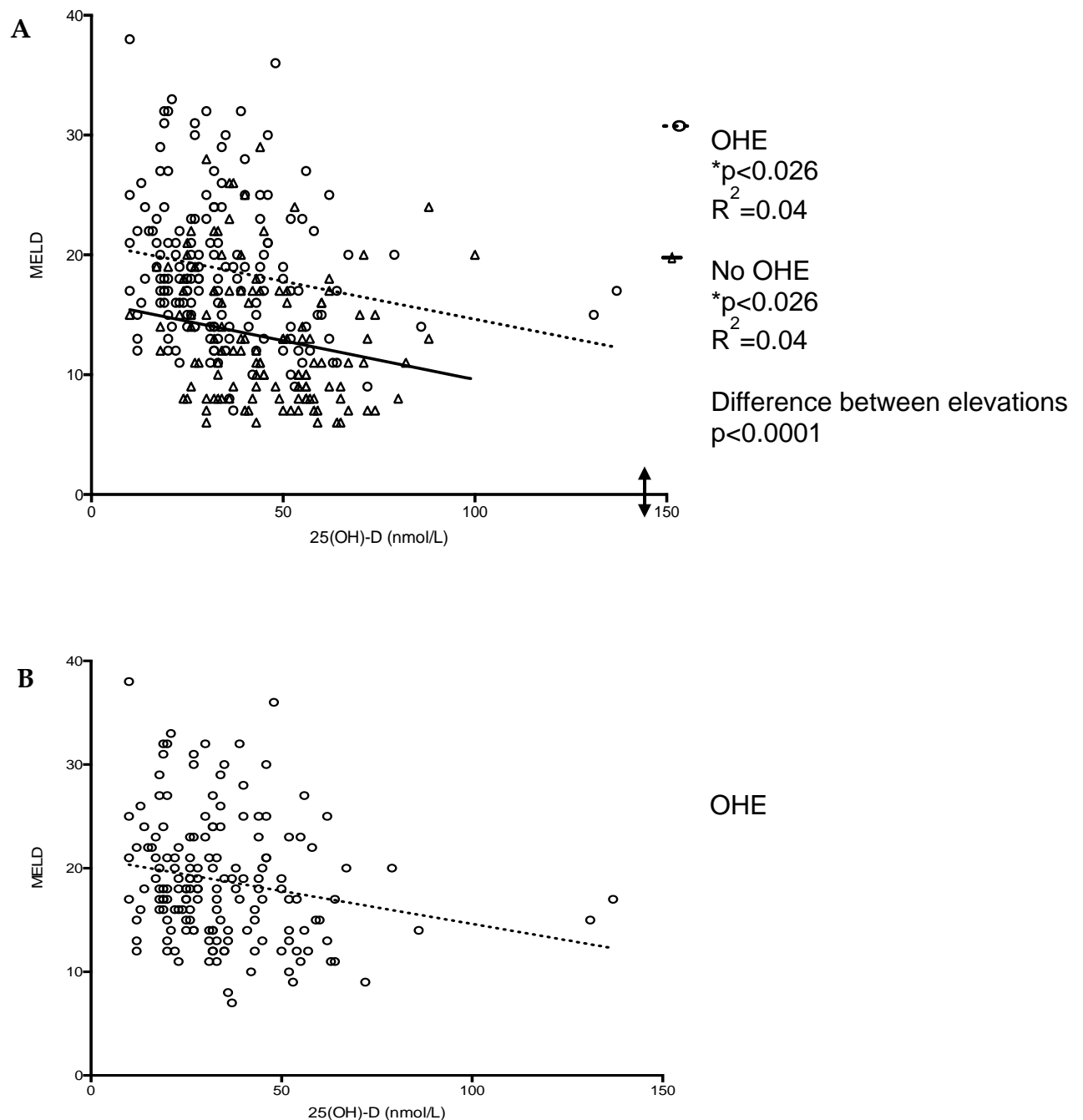
This is a similar relationship to the association of elevated serum ammonia with the development of OHE^[45]. Consequently, the presence of moderate to severe 25-OHD deficiency means OHE is more likely in patients with ESLD.

It was beyond the scope of this investigation to explore the relationship between covert HE and 25-OHD deficiency. A large proportion of patients with insufficient (78%)

or mild 25-OHD deficiency (47%) were not diagnosed with OHE. It possible that in a proportion of patients with insufficient or mild 25- OHD deficiency reduced levels of 25-OHD could be associated with the development or presence of covert HE. This is analogous to ammonia levels in ESLD which are elevated in HE but elevation does imply the presence of HE either OHE or covert HE.

- Figure 5 has been clarified as suggested by the reviewer and is now presented as Fig 5A,B,C and the figure legend has been altered to reflect this change:

Fig 5. Overt HE, disease severity and 25-OHD



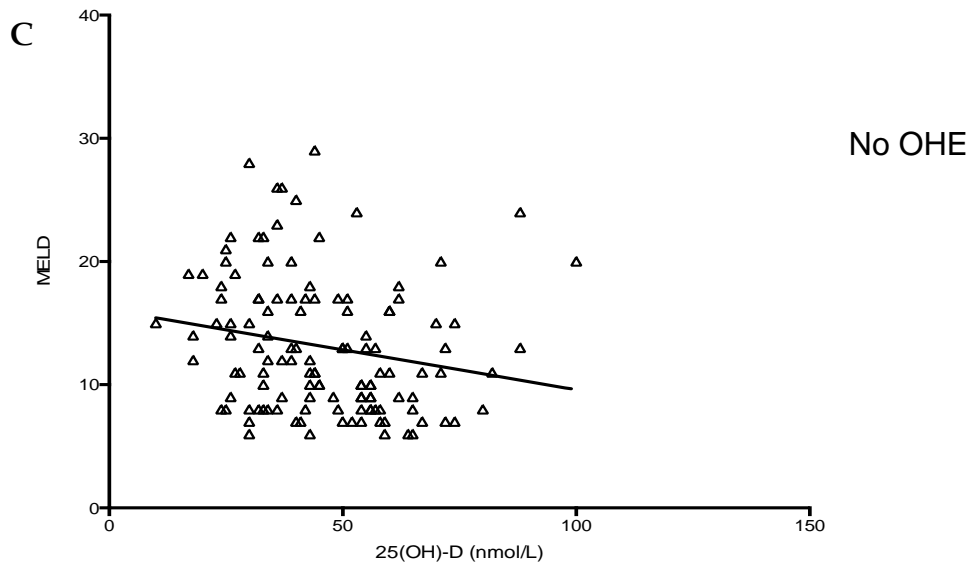


Fig 5. Overt hepatic encephalopathy, disease severity and 25-OHD.

Patients were stratified into those who had overt HE and those who did not. The combined data is presented in Panel A and the sub groups of patients with OHE in Panel B and those without OHE in Panel C. Vitamin D deficiency correlates with MELD score in both patients with and without OHE. Across the range of MELD scores from 10 - 30 patients with OHE (Panel B) had significantly lower levels of 25-OHD than those who did not (Panel C).