**Letter to the Editors**

**Stepwise diagnosis in covert hepatic encephalopathy: critical flicker frequency and MELD-score as a first-step approach**

**– replication and pitfalls**

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**Authorship**

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Sirs,

We read with interest the paper from Greinert *et al*.1 on the utility of a model encompassing the Model of End-stage Liver Disease (MELD) score and the Critical Flicker Frequency (CFF) for diagnosing covert hepatic encephalopathy (HE).

We attempted to replicate their findings in a cohort of 110 patients with cirrhosis, classified on the basis of West Haven criteria2 and the Psychometric Hepatic Encephalopathy Score,3 as neuropsychiatrically unimpaired (n=72) or as having minimal HE (n=20) or Grade 1 HE (n=18); the latter two groups were combined to form a covert HE subgroup (n=38). The MELD score was calculated using the most up-to-date definition, while CFF was measured using a Lafayette Flicker Fusion Instrument (Model 12021).

In line with the published findings, we also observed significant differences in the Child-Pugh class, MELD score, International Normalised Ratio, serum sodium, plasma albumin and the CFF between unimpaired patients and those with covert HE; however, in our cohort, serum creatinine levels were comparable between the two groups whilst the serum bilirubin levels differed significantly (Table S1).

We applied the proposed CFF/MELD model using the same introduced variables as in the published paper and confirmed that both MELD and CFF were significantly and independently associated with covert HE in the final model: *viz.* MELD: Odds Ratio(OR) 95% (Confidence Interval [CI]) 1.18 (1.04-1.35); *P* = 0.013; CFF: 0.87 (0.79-0.95); *P* = 0.002. The authors of the published paper used receiver operator characteristics to identify the best cut-off values for the independent predictors, employed a custom syntax in SPSS to allow extra weight to be given to false negative results (2:1) (C Ripoll, personal communication). However, this software is not generally available and insufficient information was supplied in the methods section of the paper to allow us to replicate their technique for finding the best cut-off values.

Our inability to replicate these findings because of the unavailability of the required software/insufficient methodological detail is a concern. Of greater concern, however, is the use of the overt/covert classification of HE. Covert HE is a term used to encompass both minimal HE and Grade 1 overt HE. However, there is clear evidence from recent papers that these patient subgroups are clearly discernible as distinct entities within the covert grouping..4,5 Indeed, we were able to show this same distinction within our current population; most notably the minimal and Grade 1 HE patients differed significantly in relation to the main components of the proposed diagnostic model, namely the degree of hepatic decompensation and mean CFF values (Table 1).

The classification of patients as ‘covert’ is, therefore, intrinsically flawed; it encompasses a heterogeneous population, the composition of which is likely to differ between centres. It would, therefore, be of interest for Greinert *et al*.1 to look separately at the results for their patients withminimal HE and Grade I HE and gauge the validity of their diagnostic criteria accordingly. A tool for diagnosing minimal HE, developed along the same lines, would be much more appropriate and would undoubtedly be welcomed.

**References**

1. Greinert R, Ripoll C, Hollenbach M, Zipprich A. Stepwise diagnosis in covert hepatic encephalopathy: critical flicker frequency and MELD-score as a first-step approach. *Aliment Pharmacol Ther* 2016;**44**:514–21.

2. Conn HO, Leevy CM, Vlahcevic ZR, *et al*. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial. *Gastroenterology* 1977;**72**:573-83.

3. Marks ME, Jackson CD, Montagnese S, *et al.* Derivation of a normative UK database for the psychometric hepatic encephalopathy score (PHES): confounding effect of ethnicity and test scoring. J Hepatol 2008;**48**(Suppl 2):S119.

4. Montagnese S, Balistreri E, Schiff S, *et al*. Covert hepatic encephalopathy: agreement and predictive validity of different indices. *World J Gastroenterol* 2014;**20**:15756-62

5. Thomsen KL, Macnaughtan J, Tritto G, Mookerjee RP, Jalan R. Clinical and pathophysiological characteristics of cirrhotic patients with grade 1 and minimal hepatic encephalopathy. PLOS ONE. 2016 Jan 8;11(1):e0146076.

**Table 1: Baseline characteristics of the patients with cirrhosis classified as covert hepatic**

**encephalopathy, by component subgroup**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable** | **Covert HE****(n=38)** | **Minimal HE****(n=20)** | **Grade 1 HE****(n=18)** | **Significance\*****(P)** |
| **Age** | 58.4±12.2 | 56.0±13.2 | 61.2±10.5 | 0.19 |
| **Male**, n (%) | 24 (63) | 14 (70) | 10 (56) | 0.50 |
| **Alcoholic aetiology**, n (%) | 28 (74) | 16 (80) | 12 (67) | 0.47 |
| **Ascites,** n (%) | 17 (45) | 6 (30) | 11 (61) | 0.10 |
| **Bilirubin** (µmol/L) | 27.9±21.7 | 25.8±25.0 | 30.4±17.7 | 0.52 |
| **INR** | 1.4±0.4 | 1.4±0.2 | 1.5±0.5 | 0.31 |
| **Creatinine** (µmol/L) | 74.2±22.7 | 72.4±16.3 | 76.3±28.9 | 0.60 |
| **Sodium** (mmol/L) | 138.4±4.8 | 138.0±4.8 | 138.8±5.2 | 0.76 |
| **AST** (IU/L) | 44.0±20.2 | 38.7±15.8 | 49.9±23.2 | 0.09 |
| **Albumin** (g/L) | 37.2±5.0 | 38.5±5.5 | 35.9±4.1 | 0.11 |
| **Child Pugh Class**, n (%) |  |  |  | 0.04 |
| A | 14 (37) | 11 (55) | 3 (17) |  |
| B | 20 (53) | 8 (40) | 12 (67) |  |
| C | 4 (11) | 1 (5) | 3 (17) |  |
| **MELD** | 12.1±4.0 | 11.0±3.5 | 13.2±4.3 | 0.09 |
| **CFF** (Hz) | 28.1±7.7 | 31.9±3.8 | 23.9±8.8 | 0.003 |

Data are Mean±1SD. AST = Aspartate Aminotransferase; CFF = Critical Flicker Frequency; HE = Hepatic Encephalopathy; INR = International Normalised Ratio; MELD = Model of End-stage Liver Disease

\*Significance of the difference between patients with minimal HE and Grade 1 HE

**Table S1:**

**Baseline characteristics of the patients with cirrhosis, by neuropsychiatric status**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variable** | **Unimpaired** (n=72) | **Covert HE** (n=38) | **Significance****(P)** |
| **Age** | 56.2±10.7 | 58.4±12.2 | 0.320 |
| **Male**, n (%) | 43 (60.0) | 24 (63) | 0.730 |
| **Alcoholic aetiology**, n (%) | 54 (75) | 28 (74) | 0.880 |
| **Ascites**, n (%) | 10 (14) | 17 (45) | <0.001 |
| **Bilirubin** (µmol/L) | 18.5±16.5 | 27.9±21.7 | 0.0068 |
| **INR** | 1.3±0.3  | 1.4±0.4 | 0.0025 |
| **Creatinine** (µmol/L) | 73.5±18.0 | 74.2±22.7 | 0.85 |
| **Sodium** (mmol/L) | 140.7±3.1 | 138.4±4.8 | 0.044 |
| **AST** (IU/L) | 41.0±32.2 | 44.0±20.2 | 0.60 |
| **Albumin** (g/L) | 43.4±6.7 | 37.2±5.0 | <0.001 |
| **Child Pugh Class**, n (%) |  |  | <0.001 |
| A | 60 (83) | 14 (37) |  |
| B | 12 (17) | 20 (53) |  |
| C | 0 (0) | 4 (11) |  |
| **MELD** | 9.8±3.1 | 12.1±4.0 | 0.001 |
| **CFF** (Hz) | 33.3±4.8 | 28.1±7.7 | <0.001 |

Data are Mean±1SD. AST = Aspartate Aminotransferase; CFF = Critical Flicker Frequency; HE = Hepatic Encephalopathy; INR = International Normalised Ratio; MELD = Model of End-stage Liver Disease

\*Significance of the difference between patients with minimal HE and Grade 1 HE