

## How to diagnose hepatic encephalopathy in the emergency department

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### ABSTRACT

**Introduction.** Blood ammonia-measurements are often performed in the emergency departments to diagnose or rule out hepatic encephalopathy (HE). However, the utility and correct interpretation of ammonia levels is a matter of discussion. At this end the present prospective study evaluated whether blood ammonia levels coincide with HE which was also established by the West Haven criteria and the critical flicker frequency, respectively. **Material and methods.** In 59 patients with known cirrhosis ammonia-levels were determined and patient were additionally categorized by the West-Haven criteria and were also evaluated psychophysiologically using the critical flicker frequency, CFF for the presence of HE. **Results.** When false positive and false negative results were collapsed the determination of blood ammonia levels alone resulted in 40.7% in a misdiagnoses of HE compared to the West-Haven criteria (24/59 when using West-Haven criteria, 95% confidence interval [CI], 28.1% to 54.3%) and 49.2% when compared with the results of the CFF (29/59, when using CFF, 95% CI, 35.9% to 62.5%). **Discussion.** Ammonia blood levels do not reliably detect HE and the determination of blood ammonia can not be regarded a useful screening test for HE. Its use as sole indicator for a HE in the Emergency Department may frequently result in frequent misinterpretations.

**Key words.** Ammonia. Critical flicker frequency. Hepatic encephalopathy. Liver cirrhosis. West Haven criteria

### INTRODUCTION

Hepatic encephalopathy (HE) reflects a wide spectrum of neuropsychological features including sleep dysfunction, psychomotor slowing and attention deficits seen in patients with liver dysfunction after exclusion of other known brain disease.<sup>1</sup> HE is divided into two primary components: overt HE (oHE) which is usually classified into four stages according to the West-Haven-criteria (Table 1) and minimal HE (mHE).<sup>2-3</sup>

The prevalence of HE in cirrhosis is high when all stages of HE are considered and can be diagnosed in up to 80% of all cirrhotic patients.<sup>1</sup> Since this condition is associated with poor quality of life and a high

risk of traffic violations and accidents, diagnostic screening must be performed routinely.<sup>4</sup> Furthermore, once the diagnosis of HE is confirmed, an extensive search for potential precipitating factors should be performed including gastrointestinal bleeding, sepsis and dehydration.<sup>1,4</sup> Therefore, HE represents an important index complication of cirrhosis and should be diagnosed as soon as possible.

Several criteria have been used to diagnose the severity of HE clinically (e.g. West-Haven criteria) and technically using for example psychometric tests (e.g. the Portosystemic-Encephalopathy-Syndrome test, PSE) and psychophysiologic tests such as critical flicker frequency (CFF).<sup>2-3,5-6</sup> Since ammonia has been regarded as the key precipitating factor, plasma ammonia levels are used widely in patients with cirrhosis and altered mental status to diagnose HE.<sup>7-9</sup> It represents a common conception that increased ammonia levels in a cirrhotic patient can confirm, or rule out, HE. However, the degree of correlation between ammonia levels and the grading of HE continues to be controversial.<sup>8-10</sup>

When cirrhotic patients are admitted to the emergency department, HE should be diagnosed as rapid

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as possible to initiate further diagnostic steps (e.g. endoscopy to rule out potential gastrointestinal bleeding) along with specific medical treatment (e.g. lactulose/antibiotic therapy).<sup>1</sup> Especially in the emergency department, resources of medical staff and time are limited. This makes time-consuming diagnostic procedures such as PSE testing almost impossible. Therefore, detection and grading of HE in clinical practice is usually performed on clinical grounds on the basis of the West-Haven criteria or by ammonia-measurement.

The present prospective study evaluated whether elevated blood ammonia levels coincide with HE which was additionally established by the West Haven criteria and the critical flicker frequency, respectively.

## MATERIAL AND METHODS

A total of 59 patients with cirrhosis who were admitted to the Emergency Department of Munich Bogenhausen Hospital between January 2007 and January 2009 were included in the study. Cirrhosis was established by either histology or by clinical and radiographic findings. The entire etiologic spectrum of cirrhosis was included. For assessment of the severity of liver disease, Child-Pugh (CP) classification score was calculated for each patient (CP A, up to 7 points; CP B, 8-10 points; CP C, > 11 points).

### Blood tests and biochemical examinations

Since Ong, *et al.* could demonstrate that venous sampling is adequate for ammonia measurement and measuring arterial ammonia generates no additional advantage, venous blood was taken for ammonia measurements.<sup>8</sup> To measure plasma ammonia, peripheral venous blood samples were obtained immediately after admission to emergency department. Samples were drawn into heparinized vacutainer tubes, placed immediately on ice, and transported to laboratory where it were processed and analysed within 30 min after withdrawal with routine laboratory methods under good laboratory practice conditions. Normal values were defined as follows: ammonia 12-55  $\mu\text{mol/L}$ . HE was assumed when ammonia-levels were above ( $\geq$ ) the normal limit of 55  $\mu\text{mol/L}$ .

### Assessment of HE severity

In addition to the ammonia levels assessment of HE and classification of the different grades of HE

were performed according to clinical criteria [West-Haven criteria (Table 1)] and according to CFF which was determined using a portable analyzer.

The CFF was determined in a quiet, semidarkened room without distracting noises. A portable, battery-powered analyzer was used (Hepatonorm TM Analyzer®, from the Clinic for Gastroenterology, Heinrich Heine University Düsseldorf, Düsseldorf, Germany). The analyzer evokes an intrafoveal light stimulus with defined pulses of light at a wavelength of 650 nm, luminance of 270  $\text{cd/m}^2$ , and luminous intensity of 5.3 mcd. The frequency of the red light, which is initially generated as a high-frequency pulse (60 Hz) and which gives the patient the impression of a steady light, was reduced gradually until the patient had the impression that the steady light had changed to a flicker. The patient registered this change by pressing a hand-held switch. The process was repeated at least 5 times to ensure that the patient understood the procedure. For the CFF measurement the procedure was repeated 10 times and from these data, the mean values for each patient were calculated.

The appropriate cut off to identify abnormal CFF is still matter of discussion. In the pilot study by Kircheis, *et al.* the threshold of an abnormal CFF was 39 Hz when comparing healthy subjects to patients with cirrhosis and HE.<sup>3</sup> Romero-Gomez, *et al.* found the best sensitivity and specificity at 38 Hz.<sup>5</sup> Kircheis, *et al.* found an average CFF of  $36.0 \pm 1.4$  Hz in subjects with HE 1 (according to West-Haven-criteria) while the average CFF in subjects with HE 2 (according to West-Haven-criteria) was  $32.1 \pm 2.7$  Hz and HE III (according to West-Haven-criteria) was  $< 30$  Hz.<sup>15</sup> In this study, HE was either divided into low grade HE (average CFF  $\leq 39$  Hz  $\geq 35$  Hz, stage 1 according to West-Haven-criteria) or high grade HE (average CFF  $\leq 35$  Hz;  $>$  stage 1 according to West-Haven-criteria) while an average CFF  $> 39$  Hz excluded HE.

### Statistical analysis

Statistical analysis was performed descriptively using statistical software R version 2.12.0 [R Development Core Team (2010). R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org/>]. Qualitative data are presented as absolute and relative frequencies, quantitative data as mean, median, standard deviation, minimum and maximum. Exact 95% confidence intervals

**Table 1.** West-Haven criteria for hepatic encephalopathy.<sup>2</sup>

Stage	Consciousness	Intellect and behaviour	Neurologic findings
0	Normal.	Normal.	Normal examination; if impaired psychomotor testing, then mHE.
1	Mild lack of awareness.	Shortened attention span; impaired addition or subtraction.	Mild asterixis or tremor.
2	Lethargic.	Disoriented; inappropriate behaviour.	Obvious asterixis; slurred speech.
3	Somnolent but arousable.	Gross disorientation; bizarre behaviour.	Muscular rigidity and clonus; Hyper-reflexia.
4	Coma.	Coma.	Decerebrate posturing.

based on the binomial distribution were estimated for the misclassification error rates of the West-Haven criteria and CFF.

Receiver operating characteristics (ROC) analysis was conducted to assess the performance of ammonium level in the blood serum for detection of hepatic encephalopathy using West Haven criteria as gold standard (0 = negative, 1 or 2 = positive). The ROC curve –plotting sensitivity *vs.* 1-specificity using observed data values as cut-offs– and the area under the ROC curve (AUC) are presented to demonstrate the diagnostic accuracy of ammonium. The Youden-Index (= sensitivity + specificity-1) was considered to determine the ammonium level that discriminates best HE positive from HE negative patients in our data.

## RESULTS

### Cirrhotic group

59 cirrhotic subjects were included in the study [30 male, 29 female; mean age 61.1 years (SD 9.9)]. The etiology of cirrhosis was alcohol abuse in 83.1% [(48/59), hepatitis C in 8.5% (5/59), cryptogenic in 5.1% (3/59), autoimmune hepatitis in 3.4% (2/59) and hepatitis B in 1.7% (1/59)]. On the basis of CP-classification, 17.0% (10/59) of patients had stage A cirrhosis, 39.0% (23/59) had stage B and 44% (26/59) had stage C. According to West-Haven criteria, HE was absent in 39% (23/59) while HE grade 1 occurred in 30.5% (18/59), HE grade 2 in 22.0% (13/59) and HE grade 3 in 8.5% (5/59). According to CFF, no HE was absent in 20.3% (12/59) while low grade HE occurred in 30.5% (18/59) and high grade HE occurred in 49.2% (29/59).

### Comparison of HE grading according to West-Haven criteria and CFF

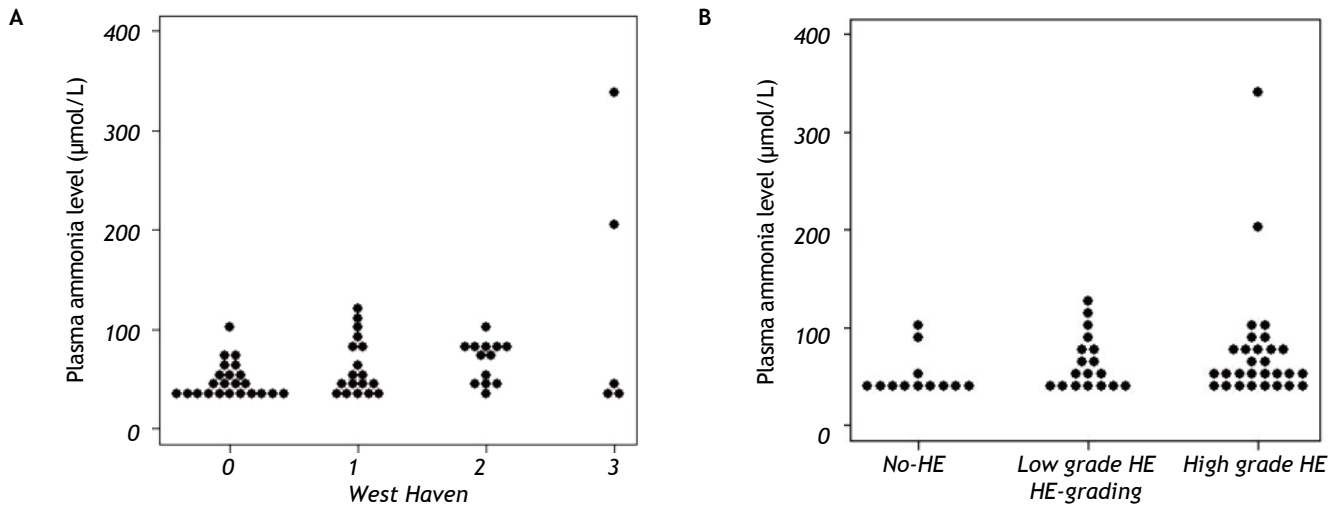
CFF detects also subjects with mHE which represents an almost subclinical condition. Therefore, measuring of CFF tended to result in a higher estimation of the severity of HE, compared to clinical classification. Furthermore, for easier comparison of the two diagnostic methods, HE grading according to CFF was divided into only 3 categories (no HE *vs.* low grade/high grade HE) instead of 4 when using West-Haven criteria. In the present study, 37.3% (22/59) of all patients were grouped into a higher HE grade by CFF than by West-Haven criteria.

Association between plasma ammonia levels and the severity of hepatic encephalopathy according to West-Haven criteria and CFF.

Mean plasma ammonia levels were increased with the severity of hepatic encephalopathy [according to West-Haven criteria and critical flicker frequency (Figures 1A-1B and Table 2)].

### HE grading according to West-Haven criteria and CFF in relation to plasma ammonia range

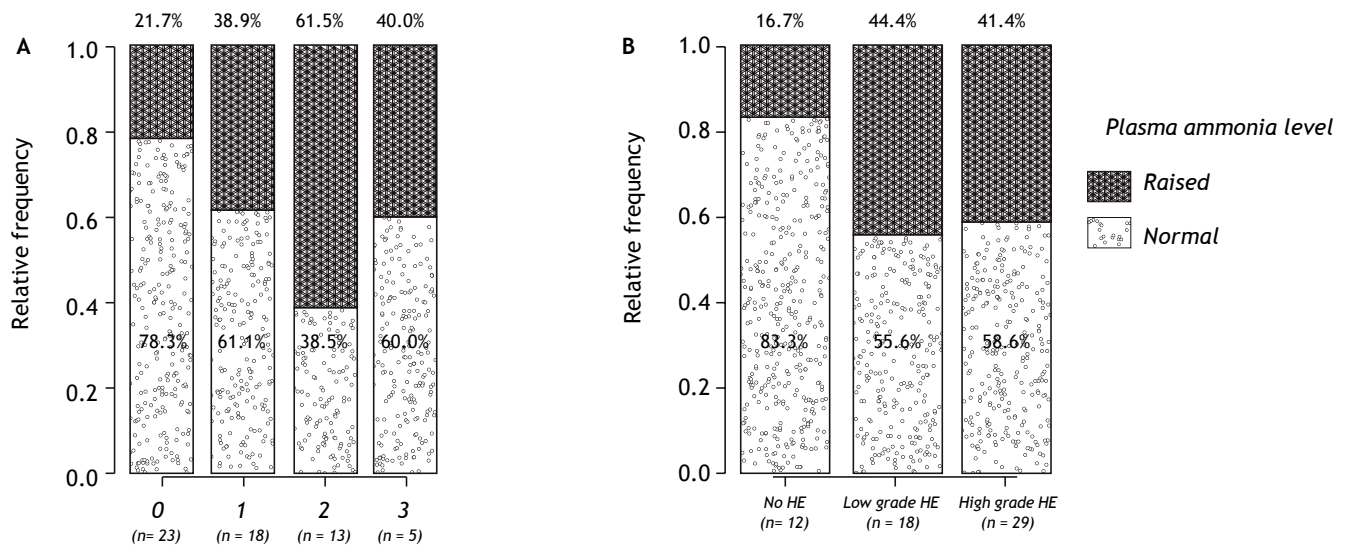
Furthermore, HE grading was performed according to West-Haven criteria and CFF in relation to plasma ammonia range [0 = normal ( $\leq 55 \mu\text{mol/L}$ ), 1 = increased ( $\geq 55 \mu\text{mol/L}$ )]. When using West-Haven criteria for HE grading, 21.7% (5/23) of cirrhotic patients without HE showed plasma ammonia values above the normal range. Conversely, in subjects with grade 1 according to the West Haven criteria, ammonia levels were within the normal limit in 61.1% (11/18) while in subjects with grade 2 in 38.5% (5/13) and in grade 3 in 60% (3/5), respectively



**Figure 1.** Plasma ammonia levels ( $\mu\text{mol/L}$ , y-axis) in association with West-Haven criteria (A. West-Haven criteria 0-3, x-axis) and HE-grading according to critical flicker frequency (B. 0 = no HE, 1 = low grade HE, 2 = high grade HE; x-axis).

**Table 2.** Association between plasma ammonia levels ( $\mu\text{mol/L}$ ) and the severity of hepatic encephalopathy according to West-Haven criteria (WHC) and critical flicker frequency (CFF).

	n	Mean ( $\mu\text{mol/L}$ )	Median ( $\mu\text{mol/L}$ )	SD	Minimum ( $\mu\text{mol/L}$ )	Maximum ( $\mu\text{mol/L}$ )
HE grade 0 (WHC)	23	37.26	31	17.965	21	92
HE grade 1 (WHC)	18	52.72	39.5	28.725	24	114
HE grade 2 (WHC)	13	57	66	20.228	25	88
HE grade 3 (WHC)	5	122	34	138.512	24	334
HE grade 0 (CFF)	12	35.58	26.5	22.411	21	92
Low grade HE (CFF)	18	50.94	41	27.875	21	114
High grade HE (CFF)	29	62.52	42	61.938	24	334



**Figure 2.** Percental distribution of plasma ammonia levels [normal range  $\leq 50 \mu\text{mol/L}$  (white), raised  $> 50 \mu\text{mol/L}$  (grey), y-axis] in correlation with West-Haven criteria 0-3, x-axis (A) and CFF grading (B).

(Figure 2A). When CFF was used for HE grading, 16.7% (2/12) of cirrhotic patients without HE showed plasma ammonia values above the normal range while 55.6% (10/18) with low grade HE and 58.6% (17/29) with high grade HE had plasma ammonia within the normal limit, respectively (Figure 2B).

The overall usefulness of blood ammonia levels to indicate HE was determined by collapsing false negative (ammonia normal but HE present) and false positive (ammonia elevated but no HE on the basis of the West-Haven criteria or CFF). Compared to the West-Haven Criteria, 40.7% (24/59 patients, 95% confidence interval [CI], 28.1% to 54.3%) and compared to the CFF 49.2% (29/59, when using CFF, 95% CI, 35.9% to 62.5%) would have been misdiagnosed when only ammonia testing was performed to assess HE.

When West-Haven criteria were defined as a gold standard for diagnosis of HE.

- Diagnostic accuracy of blood ammonia was 59.3% [95% CI = 45.7 to 71.9%; sensitivity 47.2% (95% CI = 30.4 to 64.5%), specificity 78.3% (95% CI = 56.3% to 92.5%)].  
Calculation of positive predictive value (PPV) was 77.3% (54.6 to 92.2%) while negative predictive value (NPV) was 48.6% (31.9 to 65.6%).
- Diagnostic accuracy of CFF was 74.6% [95% CI = 61.6 to 85.0%; sensitivity 94.4 (95% CI = 81.3

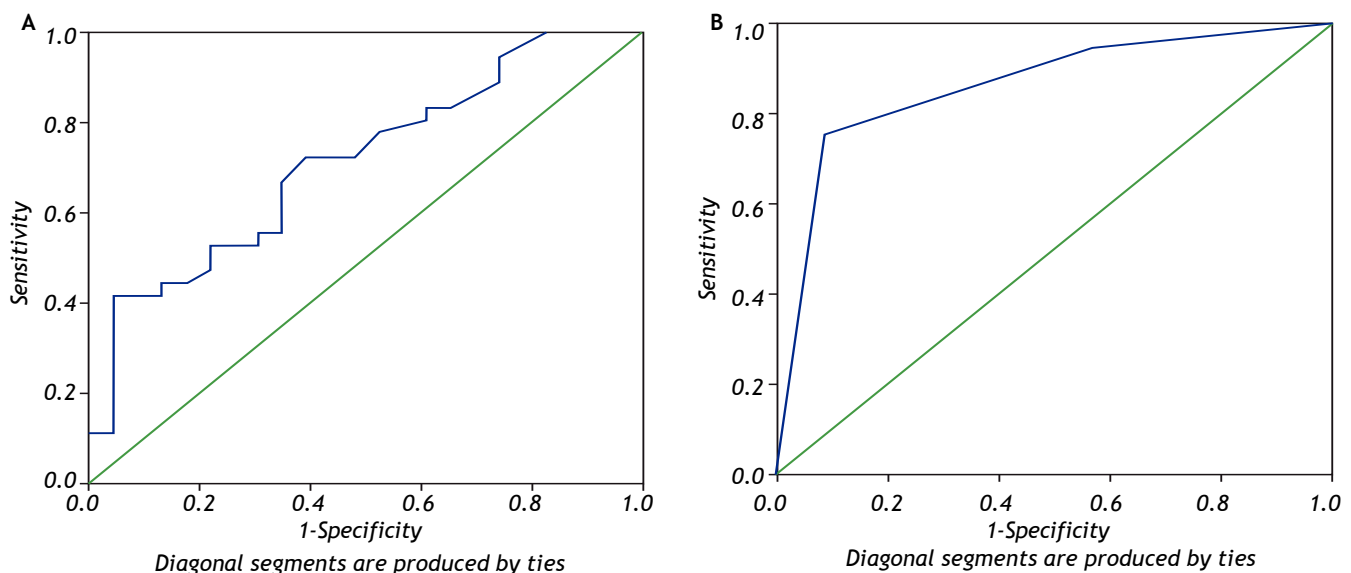
to 99.3%), specificity 43.5% (95% CI = 23.2 to 65.5%)].

Calculation of PPV was 72.3 % (57.4 to 84.4%) while NPV was 83.3% (51.6 to 97.9%).

ROC curve analysis for HE-grading according to West-Haven criteria revealed an area under the curve (AUC) of 0.71 (95%-KI: 0.58 to 0.85) while AUC of ROC curve analysis for HE-grading according to CFF was 0.861 (Figures 3A-3B).

Calculation of Youden-Index to calculate the optimal diagnostic cut off revealed a plasma ammonia value of 65.5  $\mu\text{mol/L}$  which is higher than the normal range according to the reference values of our laboratory. This ammonia level had a specificity of 95.7% (22 out of 23 patients without HE were categorized correctly) but a low sensitivity of 41.7% (only 15 out of 36 patients with HE were classified as being encephalopathic).

Since the synergistic role of inflammation and infection in modulating the cerebral effects of ammonia has been shown to be important and since it has been recognized that infection impairs brain function both in the presence and absence of liver disease, Mann-Whitney-U-test was performed to compare increased ammonia values with the occurrence of infections (obtained by standard microbiological procedures including mainly spontaneous bacterial peritonitis, pneumonia and urogenital infections) and inflammatory parameters including leucocyte count and C-reactive protein [(CRP)<sup>13-15</sup>]. Mann-



**Figure 3.** ROC curve analysis for HE-grading according to A. West-Haven criteria [AUC = 0.71 (95%-KI: 0.58 bis 0.85)] and B. CFF (AUC = 0.861).

Whitney-U-test revealed no significant correlation between patients with infections and without and blood ammonia levels ( $p = 0.056$ ). Additionally, there was no correlation between normal and increased inflammatory parameters and blood ammonia levels ( $p = 0.553$ ).

## DISCUSSION

The disturbance of consciousness in patients with advanced liver disease is a common feature in the emergency departments and usually blood ammonia levels are considered a major diagnostic hint to diagnose hepatic encephalopathy. However, while increased ammonia levels might be indicative for advanced liver disease, other factors than the disturbed liver function might contribute to elevated blood levels. The accuracy of ammonia determination is influenced by many factors including phlebotomy technique (use of tourniquets), rapid laboratory analysis on ice, arterial or venous sampling and fasting periods which should be always considered when interpreting results.<sup>1,2,11</sup> Additionally, ammonia levels can be influenced by many non-hepatic conditions, e.g. chronic renal disease, cigarette smoking or heavy exercise. Thus, factors independent from liver dysfunction could affect ammonia levels. However, Ong et al. showed that venous ammonia levels correlate with the severity of HE.<sup>8</sup>

Ammonia has been regarded as one of the major pathogenetic factors of cerebral dysfunction in HE, and astrocytes have been the most commonly affected cells.<sup>1,4,7</sup> Therefore, despite discrepant results from clinical studies, diagnosis of HE by plasma ammonia testing is considered also to be an adequate diagnostic tool.<sup>8-9</sup> The use of blood ammonia levels represents a widespread reality in the emergency department and on the wards, especially since ammonia does not follow a circadian rhythm and can be obtained easily together with the other standard laboratory parameters. For instance at the Bogenhausen Academic Teaching Hospital more than 1,000 ammonia measurements were performed in the clinical laboratory in patients suffering from chronic liver diseases in 2010 with the Emergency Department the unit initiating most orders (performance report 2010, central clinical laboratory, Munich Municipal Hospital Group). Recently, we published a survey demonstrating that blood ammonia levels are popular to diagnose and monitor the treatment of hepatic encephalopathy even in the group of gastroenterologists and hepatologists

in Germany.<sup>12</sup> In this study 60% of the respondents performed ammonia analysis in all of their cirrhotic patients but further psychophysiological testing such as CFF was not used regularly.

However, the blood ammonia levels correlate only weakly with cerebral dysfunction in hepatic encephalopathy. In the present study, we could show that false negative and false positive results occur frequently: performing HE grading in relation to serum ammonia range, resulted in an incorrect HE classification in up to 50% of the study population (40.7%, when using West-Haven criteria and 49.2%, when using CFF as reference method for HE grading) (Figure 2A-2B).

Performing ROC curve analysis revealed an AUC of 0.71 which shows an only moderate diagnostic accuracy of blood ammonia (Figures 3A-3B). In 15 out of 16 subjects with an ammonia value  $> 65.5 \mu\text{g/L}$  HE (according to West-Haven criteria) could be diagnosed which represents a high PPV. However, also 21 out of 43 patients with an ammonia value  $< 65.5 \mu\text{g/L}$  were suffering from HE which demonstrates a low NPV. Therefore, high blood ammonia levels should raise suspicion towards the occurrence of HE while a low value can not rule out HE.

Felipo, *et al.* could demonstrate that the combination of certain levels of hyperammonemia and inflammation (which was measured by inflammatory cytokines IL-6 and IL-18) is enough to induce cognitive impairment as assessed by of psychometric testing, even without liver disease.<sup>13</sup> They showed that in patients with liver diseases, cognitive impairment may appear before progression to cirrhosis if hyperammonemia and inflammation are high enough.<sup>13</sup> Since clinical studies have examined the importance of inflammation and infection in modulating the manifestation of symptoms of HE in acute liver failure and patients with cirrhosis and minimal/low grade HE, Shawcross et al. performed a prospective study of patients with cirrhosis admitted to a liver Intensive Care Unit where high grade HE was the primary indication for admission collecting various microbiological data.<sup>14</sup> Their data supports an association between infection and not ammonia, in patients with cirrhosis that develop severe HE.<sup>14</sup> Altogether, one can postulate a synergistic role of inflammation and infection in modulating the cerebral effects of ammonia.<sup>15</sup> Shawcross, *et al.* describe a neutrophil dysfunction in the presence of ammonia which contributes to oxidative stress and systemic inflammation. This may further exacerbate the cerebral effects of ammonia and potentially reduce the capacity of the neutrophil to fight microbial attack.<sup>15</sup>

In our study, Mann-Whitney-U-test revealed no significant correlation between patients with infections and without and blood ammonia levels ( $p = 0.056$ ). Additionally, there was no correlation between normal and increased inflammatory parameters and blood ammonia levels ( $p = 0.553$ ).

Our findings support the final report of the working party at the 11th world congresses of gastroenterology ammonia testing was described as a potential diagnostic tool which, however, correlates poorly with symptoms of HE.<sup>2</sup> That is obviously the consequence of the fact that many cases of hepatic encephalopathy result from a defective liver function in addition to other contributing factors like infection or dehydration. Thus, since HE affects many features of every day life e.g. driving ability, alertness, social interaction, and communication a reliable and simple diagnostic test to be performed within the Emergency Department is necessary. In this respect, critical flicker frequency which is easy to perform, reliable, and accurate is an excellent global assessment for the presence of hepatic encephalopathy in the Emergency Department.

#### CONFLICTS OF INTEREST AND SOURCE OF FUNDING

None.

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