Research Article

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The role of inflammation in covert HE

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Psychometric tests, critical flicker frequency, and inflammatory indicators in covert hepatic encephalopathy diagnosis

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Abstract

Background and Aim: Hepatic encephalopathy (HE) is a frequent complication of liver diseases. Systemic inflammation is key for HE pathogenesis. The main goal of the study was to investigate the role of psychometric tests, critical flicker frequency (CFF), and comparative evaluation of inflammatory indicators for the diagnosis of covert HE (CHE).

Materials and Methods: The study was a prospective, nonrandomized, case–control study with a total of 76 cirrhotic patients and 30 healthy volunteers. The West Haven criteria were used to determine the occurrence of CHE in cirrhotic patients. Psychometric tests were applied to healthy and cirrhotic groups. CFF, venous ammonia, serum endotoxin, IL-6, IL-18, tumor necrosis factor alpha (TNF-α) levels, and hemogram parameters were evaluated for cirrhotic patients.

Results: CFF values and psychometric tests were found to accurately discriminate CHE positives from CHE negatives ($p<0.05$). When the control group was excluded, the digit symbol test and the number connection A test failed, unlike CFF and other psychometric tests. Using CFF, a 45 Hz cutoff value had 74% specificity and 75% sensitivity. Basal albumin levels ($p=0.063$), lymphocyte-to-monocyte ratio (LMR) ($p=0.086$), and neutrophil-to-lymphocyte ratio (p 0.052) were significant, albeit slightly, among CHE groups. Basal albumin levels had 50% sensitivity and 71% specificity when 2.8 g/dL was used as a cutoff value to determine CHE.

Conclusion: Both psychometric tests and CFF can be useful in diagnosing CHE. Using cytokine and endotoxin levels seems to be inadequate to diagnose CHE. Using LMR and albumin levels instead of psychometric tests for diagnosing CHE can be promising.

Keywords: Hemogram parameters; neutrophil-to-lymphocyte ratio; lymphocyte-to-monocyte ratio; mean platelet volume; basal albumin levels; IL-6; IL-18; TNF-α; 3-nitrotyrosine; serum endotoxin.

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Introduction

Hepatic encephalopathy (HE) is a common complication of cirrhosis and is characterized by numerous neurological symptoms, underlying liver diseases, and various predisposing factors.[1] HE is not only a delirium or coma clinic in patients with advanced liver diseases but also a brain dysfunction caused by liver failure and/or portosystemic shunt.[2]

The West Haven criteria were used for classification. Covert HE (CHE) represents minimal and grade 1 encephalopathy, while grades 2, 3, and 4 encephalopathies are characterized as overt hepatic encephalopathy (OHE). According to both European and American guidelines, no test that accurately defines CHE exists.[3] One of the most commonly used diagnostic tools for CHE is the psychometric test, which requires a paper and pencil test (e.g., number connection and digit–number association) and a consultation with a neuropsychology specialist to score the results. This is often expensive and time consuming, and therefore most clinicians do not routinely use this series of tests for their patients.[4]

Psychometric test results can be affected by race, age, and educational status.[5] Nevertheless, these tools are subjective with limited interobserver reliability, especially for CHE, because findings such as mild hypokinesia, psychomotor slowing, and lack of attention can be easily overlooked in clinical practice.[6] Other neuropsychological tests that help to diagnose HE are critical flicker frequency (CFF) and electroencephalogram.[7] CFF is a helpful tool to assess visuomotor status. It involves a headset, a button that is directly connected to the headset via a cable, and a remote control for the operator. In the beginning, flickering light appears and vanishes at low frequency, and then the interval starts to get shorter. At the moment, the frequency of the flickering light is perceived as continuous by patients, and they are expected to push the button. The frequency value, quantified in Hertz, is reflected on the screen of the remote control for the operator. CFF is a simple, relatively reliable, and accurate test in the diagnosis and assessment of recovery of patients with MHE and does not depend on age or literacy.[8]

A series of inflammation indicators were described recently for varied clinical conditions. Examples of these new inflammation markers are serum endotoxin level, IL-1β, IL-6, IL-18, tumor necrosis factor alpha (TNF-α), and 3-nitrotyrosine.[9,10] There are limited data about these inflammatory parameters in the setting of HE. Another inflammatory marker is neutrophil-to-lymphocyte ratio (NLR), which is found to be independently correlated with a high mortality rate in cirrhotic patients.[11] We investigated if these inflammatory parameters could help to diagnose CHE.

Materials and Methods

This study was a nonrandomized case–control study performed on healthy volunteers and patients with liver cirrhosis who were followed up in the hepatology outpatient clinic in Ege. The inclusion criterion for healthy volunteers was not having a chronic or congenital disease and that for a patient group was the diagnosis with cirrhosis. The diagnosis was made based on history, physical examination, laboratory parameters, imaging studies, and liver biopsy, if necessary. On the basis of the West Haven criteria, patients with grade 0–1 HE status were identified and included in the study. The exclusion criteria were being older than 75 years or younger than 18 years, possessing any overt HE clinical signs (i.e., flapping tremor), not being literate (only for pencil and paper tests), senile tremor or accompanying neurological conditions (e.g., Parkinson's disease), and having auditory or visual disturbances (i.e., hypermetropia) (for pencil and paper test and CFF). Informed written consent was obtained from each patient and healthy individuals before any intervention.

CFF and Psychometric Tests

Psychometric tests were applied to both healthy individuals and patients. The tests performed were the digit symbol test (DST), number connection test A (NCT-A), serial dotting test (SDT), and line tracing test (LTT). Tests were performed in a proper room, far from any disturbance, such as noise and darkness. Each test was explained to patients, and a sample test was performed by participants before starting the actual test. For all these pencil and paper tests, the duration of completion of each test by each patient was noted and evaluated as described elsewhere.[12]

CFF (HepatonormTM Analyzer; R&R Medi-Business Freiburg GmbH, Freiburg, Germany) was operated with the assistance of investigators in the same room. Patients were asked to push the button in their hands when they perceived the flickering red light at the center of the headset screen as continuous. Each patient performed CFF nine times continuously. The mean value, which was reflected on the remote control screen by the CFF software, was taken into account after finishing nine sets.

Laboratory Work-Up

After at least 12 h of fasting, peripheral venous blood samples were collected from both patients and controls at 8:00 am. These samples were stored for 20 min for clotting. Then, they were centrifuged for about 10 min at 1500 g. The separated sera were stored immediately for equal periods in the freezer at -80 °C [median 12 (1–16) weeks] for both controls and cirrhotic patients.

Determination of Inflammatory Parameters in Serum and Plasma

Values of IL-6, IL-18, TNF-α, and 3-NT were determined using enzyme-linked immunoassay (ELISA) (BD OptEIA™ Human ELISA Kit II, BD Biosciences, Texas, USA). Serum endotoxins were also measured using ELISA (Lot No.: 201711, Rel Assay Diagnostics, Gaziantep, Turkiye). Blood samples were obtained from all participants for cytokines and endotoxin levels. Results were read with spectrophotometry (Thermo Scientific™ Varioskan™ Flash Multimode Reader) at 450 nm; optical density (OD) values were also noted. OD values for IL-1β, IL-6, IL-18, and TNF-α were directly proportional to their serum concentration levels. Only 3-NT serum concentrations were inversely proportional to OD values on the basis of serum concentration levels.

Hemogram samples were obtained for inflammatory parameters to assess mean platelet volume (MPV), lymphocyte-to-monocyte ratio (LMR), and NLR. Venous plasma ammonia was also analyzed in blood samples. Blood samples were also obtained to assess liver function and for routine follow-up. Widely used biochemical parameters such as albumin, total bilirubin, CRP, sodium levels, and INR were also investigated. These hemogram, ammonia, INR, and biochemical samples were obtained only from cirrhotic cases. All serum samples were taken simultaneously at the time of performing CFF and psychometric tests.

Statistical Analyses

Statistical analyses were performed using Windows SPSS program (version 25.0, SPSS, Inc., Chicago, IL). The Kolmogorov–Smirnov test and the Shapiro–Wilk test were used to analyze whether the data were normally distributed. For nonnormally distributed data, median and min–max values were analyzed, whereas mean and standard deviation were analyzed for normally distributed data. To compare normally distributed data, Student's t test was used, and for the comparison of nonnormally distributed data, the Mann–Whitney U test was used. The Chi-squared test or Fisher's exact test was used to assess the categorical variables. Post hoc analysis was performed to identify the differences between the groups. The Bonferroni correction was also applied. To analyze the accuracy of CFF and each psychometric test in three separate groups (Control, CHE, and non-CHE), ANOVA and the Kruskal–Wallis test were used. The receiver operating characteristic curve was used to graphically determine sensitivity and specificity.

Ethical Approval

As stated in the 1964 Helsinki declaration and its subsequent amendments, all methods including human subscribers in our study were carried out in compliance with the ethical standards of the national research committee. Written informed consent was obtained from all participants included in this study. Ethics committee approval was obtained for the study from the clinical trials ethics committee of Ege University Faculty of Medicine, a tertiary level health care center, with decision number 17-4.1/21 on July 5, 2017.

Results

This study included 76 cirrhotic patients and 30 volunteers. Of 76 patients, 41 were diagnosed as Covert HE clinic positive, and 35 were diagnosed as Covert HE clinic negative according to the West Haven criteria.

Age has an effect on PHES studies, but because of the lack of younger cirrhotic patients, the statistical result was not significant. Similarly, CFF results, age, and MELD-Na scores were found to be insignificant factors for both healthy and cirrhotic subgroups when using multivariant analysis. Characteristics of the whole study group are given in Table 1.

CFF results were statistically significant in discriminating CHE positives from negatives (p=0.001) and from healthy individuals (p=0.000). There was no statistically significant difference between healthy individuals and patients without CHE clinics.

A 38 Hz median level was obtained using the CFF test for CHE positives on the basis of the West Haven criteria. CHE negatives had 48.3 Hz median level, whereas healthy subjects had 48.4 Hz. Using a cutoff value of 45 Hz, CHE positives and negatives were differentiated, with 74% specificity and 75% sensitivity (Fig. 1).

Table 1. Baseline characteristics and results for the study group

	Control (n=30)	No CHE (n=35)	CHE (n=41)	Total (n=106)
Age (18–75)	41.5±13.3	59.5±11	59.6±11.8	53.5±12
Sex (M/F)	15:15	16:19	20:21	51:55
CFF (Hz)	48.4±2.4	47.8±5.6	40±6.6	44.4±6.8
SDT (s)	34.4±8.8	69.6±43.3	101.4±54.5	68.4±48.6
NCT-A (s)	29.2±8.1	96.8±73.6	113.7±85.7	77.3±72.8
LTT (s)	25.4±8.8	46±22.5	73.5±35.2	48.4±31.6
DST	145±57.1	262.8±174.4	570±486.1	311±337.6
IL-6	46.2±72.5	39.8±53.6	51.4±85.4	45.8±70.5
IL-18	85.3±124.2	75.8±97.8	93±143.1	84.7±121.7
TNF-α	22.4±40.9	20.2±45.2	24.3±37.4	22.3±41.1
3-NT	26.4±40.9	26.4±9.2	25.8±9.2	26.2±19.7
Endotoxin	74.1±183.9	96.1±218.4	56±150.5	75.4±184.2
CPS	*	6.04±1.32	7.72±1.51	6.9±1.64
MELD-Na	*	11.03±4.61	10.73±4	10.87±4.26

Values are expressed as mean±SEM. CHE: Covert hepatic encephalopathy; M: Male; F: Female; CFF: Critical flicker frequency; SDT: Serial dotting test; NCT-A: Number connection test A; LTT: Line tracing test; DST: Digit symbol test; IL: Interleukin; TNF-α: Tumor necrosis factor alpha; NT: Nitrotyrosine; CPS: Child Pugh score; MELD: Model for end-stage liver disease.

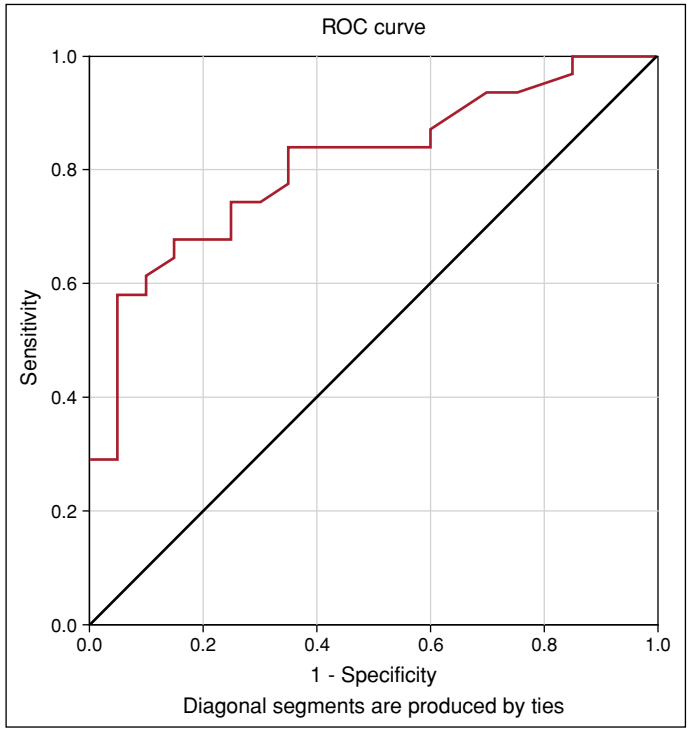

Figure 1. ROC Curve analysis for CFF results.
ROC: Receiver operating characteristic; CFF: Critical flicker frequency.

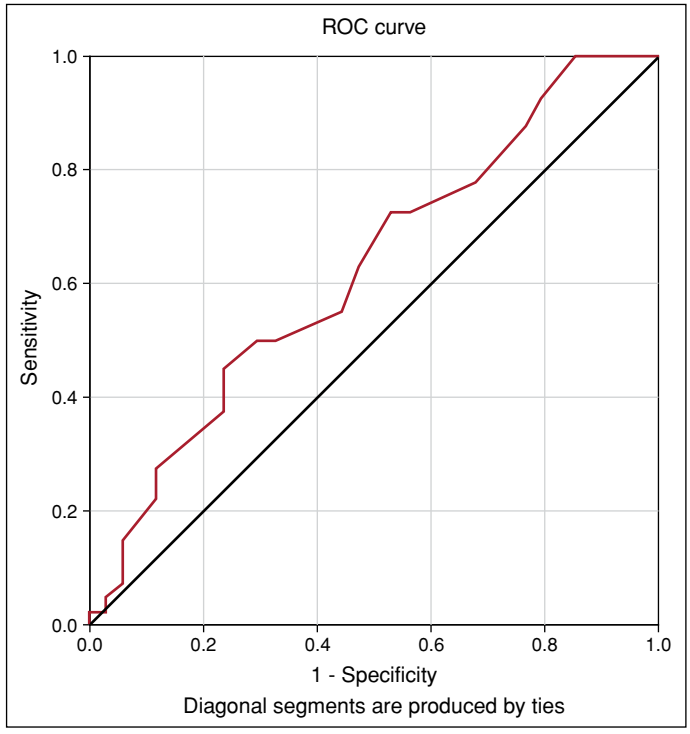

Figure 2. Base albumin levels ROC curve analysis.
ROC: Receiver operating characteristic.

SDT and LTT were able to differentiate CHE positives from negatives; however, NCT-A and DST could not. After adding the control group into the analysis, statistically significant results were obtained for all groups (p=0.000 for SDT, NCT-A, and LTT; p=0.002 for DST) (Table 2).

Psychometric tests were correlated with one another and results were statistically significant (p<0.05), but CFF did not have any correlation with any pencil and paper test. Also, CFF was not correlated with Child-Pugh scores and MELD-Na.

Baseline IL-6 and endotoxin levels were found to be significantly higher among cirrhotic cases than the healthy volunteers (p=0.032 and p=0.028, respectively). Baseline IL-6 and endotoxin levels were analyzed between CHE positives and negatives and no significant difference was found. Serum IL-18 and 3-NT levels did not show any significant differences between all groups. TNF-α levels were only found to be higher in healthy volunteers than in cirrhotic cases (p=0.019), and levels were not significant for CHE positives and negatives.

Table 2. Values of different parameters for CFF and psychometric tests

	Control	CHE	No CHE	p values (with CHE vs no CHE)	Kruskal–Wallis p values for all groups	Total
CFF	48.4 (40.7–51)	38 (25–54.9)	48.3 (35.8–58)	0.000	0.000	46.3 (25–58)
SDT	35 (23–56)	100 (16–236)	65 (20–170)	0.089	0.000	44.5 (16–236)
NCT-A	29 (17–44)	103 (27–360)	79.5 (23–300)	ns	0.000	36 (17–360)
LTT	26 (15–51)	64 (21–131)	38 (22–90)	0.025	0.000	37 (13–131)
DST	132 (84–296)	400 (86–1800)	208 (60–630)	ns	0.002	46.3 (29–1800)

Numbers are shown as median values per second for SDT, NCT-A, LTT, and DST and in Hertz for CFF. Minimum and maximum values are shown in parenthesis per second for SDT, NCT-A, LTT, and DST and in Hertz for CFF. CHE: Covert hepatic encephalopathy; CFF: Critical flicker frequency; SDT: Serial dotting test; NCT-A: Number connection test A; DST: Digit symbol test; LTT: Line tracing test.

No significant result was observed between CHE positives and CHE negatives regarding serum ammonia, total bilirubin, INR, CRP, and PLT values. However, albumin (p=0.063), NLR (p=0.052), and LMR (p=0.086) levels were slightly different for the discrimination of CHE positives from negatives (Table 3). Base albumin levels had 50% sensitivity and 71% specificity when 2.8 g/dL was used as a cutoff value to determine CHE (Fig. 2).

Correlation analysis was performed between blood tests, and CFF and psychometric tests. Serum albumin levels were correlated with all pencil and paper tests (SDT: p=0.024; NCT-A: p=0.018: LTT: p=0.030; DST: p=0.016). Also, LMR was correlated with all psychometric tests (SDT: p=0.005; NCT-A: p=0.003; LTT: p=0.011; DST: p=0.042). All these statistical correlations for serum albumin and LMR with psychometric tests were inversely proportional, so correlation coefficients were below zero.

Discussion

In covert HE patients, visual-spatial assessment, attention, responsiveness, inhibition of response, and psychomotor speed are diminished.[13] CHE prevalence was reported to be 30%–85% with cirrhosis.[14] The incidence of OHE in patients with cirrhosis was estimated to be 30%–50%, and it is reported that there is a 20% risk of developing OHE among cirrhotic patients per year.[15,16] This high incidence causes an economic burden for cirrhotic patients and increased hospitalization rates.[17] The economic burden associated with HE is important and increasing. A study in the USA, from 2005 to 2009, suggested the total cost of hospitalizations associated with HE increased by 55.1%.[18] In addition to negative effects on the quality of life, it was also reported that HE has direct effects on patient survival regardless of the severity of cirrhosis.[14] Interventions to CHE may increase health quality; however, our ability to identify CHE and predict progression to OHE is limited for patients with cirrhosis.[19]

As treating HE may require intensive care and frequent hospitalization linked to serious morbidity and mortality, it may be beneficial to diagnose and treat patients at a relatively subclinical stage. However, early diagnosis of covert HE is usually difficult. CHE is regarded as the preclinical stage of OHE, but when defining grade 1 HE clinic, the lack of objective findings reduces the reliability of the diagnosis. Recently, alternative tests were performed at patient bedsides. These include the inhibitory control test (performed via a computer program), EncephalApp (a smartphone or tablet application), Disease Impact Profile (an algorithm based on the symptoms reported to the patient), and the Animal Naming Test. According to some studies, the gold standard test for diagnosis of CHE is the West Haven criteria.[20,21]

Table 3. Values of baseline parameters for inflammatory markers between CHE and no CHE

	No CHE (n=35)	CHE (n=41)	p
IL-6 (pg/mL)	18.2 (0.06–211.5)	16.8 (0.06–429)	NS
IL-18 (pg/mL)	31.9 (2–410.8)	31 (3.6–597)	NS
TNF-α (pg/mL)	7.1 (0.06–210)	7.1 (0.06–132)	NS
3-NT (ng/mL)	24 (7–44)	24 (8–62)	NS
ET (U/L)	8 (6–699)	9 (5–699)	NS
PLT (μL^{-1})	102 (45–496)	100 (36–291)	NS
MPV (fL)	11 (9–12.8)	11.1 (9–13.8)	NS
NLR	2.1 (0.9–7.9)	2.8 (1–6.4)	0.052
LMR	2.9 (0.6–5.6)	2.2 (0.6–4.7)	0.086
Ser. albumin (g/dL)	4.1 (2.7–5.6)	3.8 (2.1–4.6)	0.063
Total bil. (mg/dL)	1.1 (0.28–4.5)	0.9 (0.29–5.1)	NS
INR	1.2 (0.9–2.2)	1.2 (0.9–1.6)	NS
Serum CRP	0.46 (0.03–3.54)	0.32 (0.04–2.39)	NS
Plasma Na^+	140 (130–144)	138 (131–147)	0.048

Results are shown as median values (range). CHE: Covert hepatic encephalopathy; IL: Interleukin; TNF-α: Tumor necrosis factor alpha; NT: Nitrotyrosine; ET: Endotoxin; PLT: Platelet; MVP: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; INR: International normalized ratio; CRP: C-reactive protein; Total bil.: Serum total bilirubin; Ser. albumin: Serum albumin.

In recent years, emerging data suggest that the CFF test could be useful in the diagnosis of HE. In our study, we documented that CFF could statistically significantly differentiate CHE-positive cirrhotic cases from CHE negatives and from healthy individuals. Using a 45 Hz cutoff value, CFF seems to be very helpful in diagnosing CHE, as we obtained 74% specificity and 75% sensitivity. A recent study showed that psychometric tests, which were alternative diagnostic tools for HE, have 58% sensitivity and 68% specificity in diagnosing CHE.[22] A meta-analysis including nine different studies related to CFF and diagnosis of CHE documented 61% sensitivity and 79% specificity. In this meta-analysis, the CFF cutoff value was 38–39 Hz.[23] We suggest that cutoff values for every population should be evaluated locally. After that local standardization, CFF, instead of psychometric tests, might be used as the "gold standard" for the diagnosis of CHE. In this standardization process, could the "age of patients" be a conflicting factor? We performed a multivariate analysis assessing age, and insignificant results were obtained. Another study

documented that CFF results for patients in different age groups did not differ.[8] More controlled studies will be needed in the future to clarify the cutoff value.

Regarding the current "gold standard" psychometric tests, statistically significant differences were obtained in the three groups (control, CHE positives, and CHE negatives). However, large standard deviations within each group could prevent obtaining a cutoff point for each test score or total test score, and age or education for the patient subgroups may be confounding factors. As most of the cirrhotic patients in our study group had advanced age, statistical data were not adequate to reach a conclusion. Using an age-matched control group could make the statistical analysis more significant. Regarding our results, we suggest that these tests should be evaluated with some correction factors. Although both CFF and psychometric test results showed significant differences between CHE positives and negatives, interestingly, there were no correlations between those two test results (another issue to work on).

Ammonia is still considered the most important factor in the pathogenesis of the disease. Many studies investigated plasma ammonia levels because ammonia is a key point in disease pathogenesis. Even in overt HE stages, ammonia levels are not useful for diagnosis.[24] Moreover, blood ammonia levels and the grade of HE are not correlated.[25,26] Our study documented median plasma ammonia levels of 71 µg/dL and 53 µg/dL for CHE positives and CHE negatives, but this was not statistically significant.

Systemic inflammation is key in the pathogenesis of HE;[27] therefore, molecules that exist in this process might help to diagnose the disease. A study including 55 cirrhotic patients and 26 healthy subjects suggested that IL-6 and IL-18 might be helpful for the diagnosis of CHE.[28] Although higher IL-6 and IL-18 levels were found in cirrhotic cases compared to healthy subjects in our study, interleukins failed to differentiate CHE positives from CHE negatives.

The keystone for inflammatory response, TNF-α, was also investigated in the literature; higher values of TNF-α were correlated with higher HE levels.[29] Although TNF-α levels were lower in cirrhotics than healthy controls, TNF-α levels were not able to discriminate those with or without CHE in our study. Another inflammatory marker, nitrotyrosine activity, was also investigated for whether it could be used as a diagnostic tool.[30,31] In our study, no significant results were obtained.

Albumin is a protein that is produced mainly by the liver, and its concentration decreases especially in the later stages of chronic liver diseases.[32,33] Base albumin levels in our study groups were 4.1 g/dL in CHE negatives and 3.8 g/dL in CHE positives, which is a slightly significant finding ($p=0.063$). Moreover, base albumin levels were strongly correlated with all psychometric tests ($p<0.05$). Therefore, we analyzed whether base levels of albumin could be helpful for CHE diagnosis. If an albumin level of 2.8 g/dL is used as a cutoff value, 50% sensitivity and 71% specificity were obtained (Fig. 2).

Inflammation indexes such as LMR and NLR were used to predict the prognosis of cirrhosis. Lower LMR and elevated NLR levels were associated with higher mortality in HBV-related cirrhotic patients.[34,35] NLR levels with a median value of 2.1 for CHE negatives and 2.8 for CHE positives were calculated in our study. LMR had a median value of 2.9 for CHE negatives and a median value of 2.2 for CHE positives. Although the figures did not reach statistical significance, almost significant results were obtained for both parameters (NLR: $p=0.052$; LMR: $p=0.086$). Another point that seems remarkable is the correlation of LMR results with all psychometric tests ($p<0.05$). These findings need more detailed studies with a larger number of cases.

Conclusion

Calculating endotoxin and cytokine levels does not seem to be helpful for CHE diagnosis, whereas lower albumin and LMR levels might help to alert the physician to CHE diagnosis.

Ethics Committee Approval: The Ege University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 05.07.2017, number: 17-4.1/21).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – ED, ND, ZK, USA, FG, GE, IT; Design – ED, ND, ZK, FG, GE, USA, IT; Supervision – ED, ND, ZK, FG, GE, USA, IT; Fundings – ED, ND, ZK, FG, GE, USA, IT; Materials – ED, ND, ZK, FG, GE, USA, IT, PE; Data Collection and/or Processing – ED, ND, ZK, FG, GE, USA, IT, PE; Analysis and/or Interpretation – ED, PE, TK, ND; Literature Search – ED, ND, ZK, FG, GE, USA, IT; Writing – ED, ND, ZK; Critical Reviews – ZK, FG, GE, USA, IT, ND.

Conflict of Interest: The authors have no conflict of interest to declare.

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