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# Psychiatric and Neuropsychiatric Phenotypes in Alcohol-Related Liver Disease: Clinical and Biochemical Associations

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## Abstract

Background: Alcohol-related liver disease (ALD) is frequently accompanied by psychiatric and neuropsychiatric manifestations that contribute to disease complexity. This hospital-based observational study aimed to characterize psychiatric and neuropsychiatric comorbidity patterns in a single-center series of 50 patients with ALD and to explore their associations with demographic characteristics and biochemical profiles, including serum immunoglobulin A (IgA) and immunoglobulin G (IgG). Methods: In this observational study, 50 consecutively hospitalized patients with ALD were evaluated. Neuropsychiatric manifestations—namely hepatic encephalopathy (HE, assessed clinically and graded using West Haven criteria), anxiety-depressive manifestations, delirium tremens, alcohol-related psychosis, and insomnia—were recorded based on clinical evaluation without standardized psychometric rating scales. Demographic characteristics and biochemical parameters (IgA, IgG, liver enzymes, bilirubin, albumin, INR, hemoglobin, MCV, and platelets) were compared between groups using non-parametric tests. Multivariable logistic regression was used to identify factors associated with HE. Results: HE was present in 60% of patients, anxiety-depressive manifestations in 54.0%, insomnia in 50.0%, alcoholic psychosis in 22%, and delirium tremens in 16.0%. Patients with HE exhibited significantly higher IgA (7.09 ± 2.33 vs. 4.94 ± 2.39 g/L, $p = 0.003$) and IgG concentrations (16.83 ± 3.68 vs. 13.72 ± 4.55 g/L, $p = 0.029$), alongside lower hemoglobin levels ($p = 0.025$). In multivariable analysis, age 51–70 years (OR = 11.882, 95% CI: 2.268–62.244, $p = 0.003$) and higher IgG concentrations (OR = 1.288 per g/L, 95% CI: 1.035–1.603, $p = 0.023$) remained independently associated with HE. Conclusions: Psychiatric and neuropsychiatric comorbidities are frequent in hospitalized patients with ALD. Given the observational design, lack of standardized psychometric scales, and small sample size, these exploratory findings—particularly the immunological associations—require validation in larger prospective cohorts.

**Keywords:** alcohol-related liver disease; psychiatric comorbidity; clinical phenotyping; hepatic encephalopathy; anxiety-depressive disorders; alcoholic psychosis; insomnia; delirium tremens; immunoglobulin A; immunoglobulin G

Academic Editor: Basavaraj S. Balapal

Received: 3 October 2026
Revised: 12 November 2026
Accepted: 14 November 2026
Published: 18 November 2026

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## 1. Introduction

Alcohol-related liver disease (ALD) represents an important consequence of prolonged harmful alcohol consumption and encompasses a spectrum of hepatic injury that may progress from steatosis and alcohol-associated hepatitis to fibrosis, cirrhosis, and its complications [1]. Its clinical management is particularly complex because alcohol use disorder (AUD), psychiatric comorbidities, and psychosocial difficulties frequently coexist with hepatic disease [1]. Consequently, contemporary management strategies increasingly emphasize an integrated multidisciplinary approach involving hepatology, addiction medicine, psychiatry, and psychosocial care [1].

Psychiatric comorbidity represents an important component of the clinical burden associated with ALD [2]. Recent population-level evidence indicates that several psychiatric disorders are increasingly identified among patients with ALD [2]. In a large United States database study covering the period from 2015 to 2023, the prevalence of major depressive disorder among patients with ALD increased from 28.54% to 36.37%, while the prevalence of anxiety disorders increased from 28.12% to 43.47% [2]. Moreover, differences in psychiatric comorbidity patterns were observed according to cirrhosis status and age, supporting the concept that psychiatric morbidity in ALD is heterogeneous and may vary among clinically distinct patient subgroups [2].

Depressive and anxiety manifestations are particularly relevant in chronic liver disease [3]. The current evidence supports a bidirectional relationship between liver disease and mental health, involving interconnected biological, behavioral, and psychosocial pathways [3]. Psychiatric symptoms may negatively influence health-related behaviors and continuity of care, whereas chronic liver disease may increase psychological vulnerability through biological mechanisms, symptom burden, and psychosocial factors [3]. Considerable heterogeneity has nevertheless been reported across studies [3]. In ALD specifically, a recent review found that the reported prevalence of depressive symptoms ranged from 9.00% to 34.92%, reflecting differences in patient populations and assessment methodologies [3]. These findings underline the importance of evaluating psychiatric manifestations within well-characterized ALD populations rather than considering psychiatric morbidity as a uniform complication of liver disease [3].

Hepatic encephalopathy (HE) constitutes a distinct neuropsychiatric complication of liver dysfunction and encompasses a broad spectrum of cognitive, neurological, and behavioral abnormalities [4]. Its clinical manifestations may range from subtle impairment of concentration and memory to psychomotor abnormalities, disorientation, and coma [4]. The pathophysiology of hepatic encephalopathy is multifactorial and extends beyond hyperammonemia, involving mechanisms such as neuroinflammation, oxidative stress, altered neurotransmission, systemic immune activation, and disturbances of the gut–liver–brain axis [4,5]. Anxiety, depressive manifestations, and sleep disturbances may coexist with cognitive abnormalities in patients with HE, further complicating neuropsychiatric characterization [4]. However, the relationship between HE and specific depressive or anxiety disorders remains incompletely established [6]. A systematic review evaluating the available evidence identified substantial methodological heterogeneity and emphasized the need for further research to clarify these associations [6].

Sleep disturbance represents another clinically relevant component of the neuropsychiatric spectrum observed in chronic liver disease [7,8]. Patients with cirrhosis may experience impaired sleep quality and abnormalities of the sleep–wake cycle, which can negatively affect daily functioning and quality of life [7]. More recent evidence confirms that sleep disturbances are common in chronic liver disease and that their characteristics may differ according to the etiology and severity of hepatic disease [8]. The mechanisms underlying these abnormalities are likely multifactorial and may involve interactions among liver-related physiological changes, sleep regulation, and neuropsychiatric

https://doi.org/10.3390/diseases14110428

complications [7,8]. Accordingly, insomnia and other sleep disturbances warrant specific clinical consideration when characterizing the neuropsychiatric profile of patients with liver disease [7,8].

Alcohol withdrawal introduces an additional spectrum of potentially severe neuropsychiatric manifestations [9,10]. Delirium tremens (DT) represents the most severe end of the alcohol withdrawal spectrum and combines delirium with severe withdrawal manifestations, including agitation and, in some patients, hallucinations [9]. Its prevalence has been estimated at below 1% in the general population and approximately 2% among individuals with alcohol dependence [9]. Importantly, liver disease is a frequent medical comorbidity among patients presenting with DT and may complicate clinical presentation, influence therapeutic decisions, and affect outcomes [9]. Neuroadaptive alterations associated with chronic alcohol exposure and subsequent withdrawal, particularly involving inhibitory and excitatory neurotransmitter systems, are considered central to the pathophysiology of severe alcohol withdrawal states [10].

Alcohol-related psychotic manifestations constitute another clinically distinct component of the psychiatric spectrum associated with alcohol use [11]. Acute alcoholic hallucinosis is characterized predominantly by auditory hallucinations accompanied by delusional and affective symptoms and classically develops in the context of alcohol withdrawal [11]. Despite its recognized clinical relevance, the available evidence remains comparatively limited, and the literature includes heterogeneous diagnostic terminology and relatively small clinical studies [11]. Careful clinical characterization is therefore important when distinguishing alcohol-related psychotic manifestations from delirium tremens, primary psychotic disorders, and neuropsychiatric abnormalities occurring in the context of hepatic dysfunction [11].

Beyond their clinical manifestations, patients with ALD exhibit multiple biological alterations that may contribute to interindividual heterogeneity [12,13]. Chronic alcohol exposure and liver injury are associated with disturbances involving hepatic function, inflammatory pathways, intestinal permeability, and gut–liver immune interactions [12,13]. Immunoglobulin A (IgA), a major immunoglobulin isotype within the gastrointestinal mucosal defense system, and immunoglobulin G (IgG), a primary driver of systemic humorally mediated immunity, have both been shown to undergo marked alterations in chronic liver disease due to gut dysbiosis, bacterial translocation, and hypergammaglobulinemia [12,13]. Although serums IgA and IgG are widely recognized markers of mucosal disruption and systemic immune dysregulation in liver dysfunction, their specific associations with psychiatric and neuropsychiatric phenotypes in ALD remain insufficiently characterized [12,13].

We hypothesized that intestinal barrier dysfunction and chronic immune activation in ALD, reflected by altered serum immunoglobulin concentrations (IgA and IgG), are associated with the presence and severity of neuropsychiatric manifestations, particularly hepatic encephalopathy [5,12–14].

Taken together, the current evidence indicates that the psychiatric and neuropsychiatric burden associated with ALD is heterogeneous and cannot be adequately represented by a single diagnostic category [1–4]. Hepatic encephalopathy, anxiety-depressive disorders, insomnia, alcohol-related psychosis, and delirium tremens occur within distinct, although potentially overlapping, clinical and physiological contexts [1–4,6–11]. A phenotype-oriented approach in which these manifestations are evaluated separately, while demographic, conventional biochemical, and immunological characteristics are simultaneously considered, may therefore provide a more detailed characterization of psychiatric comorbidity in patients with ALD.

Accordingly, the present study aimed to characterize the distribution of psychiatric and neuropsychiatric comorbidities in patients with an alcohol-related liver disease and

to investigate their associations with demographic characteristics and biochemical profiles. Particular attention was given to hepatic encephalopathy, anxiety-depressive disorders, delirium tremens, alcohol-related psychosis, and insomnia. Biochemical profiling included conventional hepatic and hematological parameters together with serum immunoglobulin A (IgA) and immunoglobulin G (IgG), with the primary goal of exploring whether distinct psychiatric and neuropsychiatric phenotypes were accompanied by identifiable biological patterns.

## 2. Materials and Methods

### *2.1. Study Design and Participants*

This single-center, observational study included a consecutive cohort of 50 hospitalized patients with alcohol-related liver disease (ALD) evaluated at the "Sf. Apostol Andrei" Emergency Clinical County Hospital Galati, Romania, between January 2025 and March 2025. Rather than representing a population-level cross-sectional sample, this cohort reflects a consecutive clinical series of eligible inpatients admitted during the predefined study window.

Inclusion criteria were age ≥ 18 years and an established clinical, laboratory, and imaging diagnosis of ALD (alcohol-related steatohepatitis/advanced fibrosis or liver cirrhosis). Exclusion criteria comprised active chronic viral hepatitis (HBV, HCV), co-existing autoimmune liver diseases, HIV infection, active systemic autoimmune disorders that could independently alter serum immunoglobulin levels, recent blood transfusions, or exogenous albumin administration within 30 days prior to enrollment. The sample size was determined by the total number of eligible consecutive patients admitted to the inpatient unit during the predefined study period who met all eligibility criteria and provided informed consent.

Patients categorized under "hepatopathy" ($n = 11$) represented non-cirrhotic alcohol-related liver injury (steatohepatitis and/or advanced fibrosis without overt cirrhosis). Hepatic characterization included the main liver diagnosis, presence or absence of ascites, Child–Pugh classification (evaluated in all patients, though Child–Pugh score criteria strictly apply to cirrhotic individuals), and ultrasonographic fibrosis stage evaluated using standard abdominal ultrasound equipment (GE Voluson E8,Austria) to assess liver parenchymal echogenicity, vascular pattern, and signs of portal hypertension.

### *2.2. Demographic and Clinical Assessment*

Demographic variables included age, sex, and area of residence (urban or rural). Age was analyzed both as a continuous variable and according to age categories (≤50 years, 51–60 years, 61–70 years, and >70 years).

Clinical characterization of liver disease included the main hepatic diagnosis, presence or absence of ascites, Child–Pugh classification, and ultrasonographic fibrosis stage. These parameters were used to characterize the study population and to investigate their relationships with the neuropsychiatric manifestations evaluated.

### *2.3. Neuropsychiatric Assessment*

Neuropsychiatric manifestations were evaluated upon hospital admission by attending psychiatrists and neurologists. Five manifestations were specifically recorded: hepatic encephalopathy, anxiety-depressive manifestations, delirium tremens, alcohol-related psychosis, and insomnia.

For statistical analysis, each manifestation was recorded as a dichotomous variable according to its presence or absence. No standardized psychometric rating scales (e.g., HAM-D, HAM-A) were administered; therefore, "anxiety-depressive manifestations"

represents a collective clinical term describing clinically documented affective and anxiety symptoms rather than formal diagnostic entities established via structured psychometric instruments. Delirium tremens and alcohol-related psychotic manifestations were identified based on standardized clinical presentation documented during medical assessment. Hepatic encephalopathy was clinically identified and graded according to the West Haven criteria.

Neuropsychiatric evaluations were performed by attending psychiatrists and neurologists who were blinded to the patients◎serum immunoglobulin levels, thereby minimizing ascertainment bias. All patients were explicitly informed at admission that their anonymized clinical and laboratory data would be included in this observational research study.

### *2.4. Laboratory Assessment*

Venous blood samples were collected within 24–48 h of hospital admission, concurrently with the neuropsychiatric clinical assessment. Laboratory evaluation included immunological, hepatic, coagulation, and hematological parameters.

Serums immunoglobulin A (IgA, expressed in g/L) and immunoglobulin G (IgG, expressed in g/L) were measured using quantitative immunoturbidimetric assays on an automated clinical chemistry analyzer. Reference ranges for adult serum immunoglobulins in our laboratory were 0.70–4.00 g/L for IgA and 7.00–16.00 g/L for IgG. Other parameters analyzed comprised gamma-glutamyl transferase (GGT, U/L), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), total and direct bilirubin (mg/dL), serum albumin (g/dL), international normalized ratio (INR), hemoglobin (g/dL), mean corpuscular volume (MCV, fL), and platelet count ($10^3/\mu L$).

### *2.5. Statistical Analysis*

Statistical analyses were performed using Microsoft Excel and IBM SPSS Statistics, version 31.0. Categorical variables were summarized as absolute frequencies and percentages. Continuous variables were described using the mean, standard deviation, minimum and maximum values, median, and interquartile range.

The distribution of continuous variables was assessed for normality. Non-parametric statistical methods were used: the Mann–Whitney U test for two independent groups and the Kruskal–Wallis test for three or more independent groups. Associations between categorical variables were evaluated using the chi-square test, with Fisher◎s exact test applied when expected cell frequencies were below five.

Binary logistic regression was used to investigate factors independently associated with hepatic encephalopathy. Candidate predictors were selected based on clinical relevance and univariate association ($p < 0.10$) and refined using backward stepwise elimination. Model fit was evaluated using the Nagelkerke $R^2$, Hosmer–Lemeshow test, and Area Under the ROC Curve (AUC). Given the small sample size (n = 50) and exploratory nature of the study, formal adjustments for multiple testing (such as False Discovery Rate) were not performed, and univariate biochemical correlations are reported as exploratory findings.

### *2.6. Ethical Considerations*

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the "Sf. Apostol Andrei" Emergency Clinical County Hospital Galati, Romania (approval no. 6627/08 April .2025). Prior to study enrollment, the study investigators explained the purpose of the research to all eligible patients, and signed, written informed consent was obtained from all participants (or their legal representatives where applicable).

## 3. Results

### *3.1. Characteristics of the Study Population*

A total of 50 patients with alcohol-related liver disease were included, as summarized in Table 1. The cohort comprised 42 men (84 %) and eight women (16 %). Urban residents accounted for 16 patients (32%), while 34 (68 %) originated from rural areas.

The mean age was 61.60 ± 11.52 years (median 62.50 years). Overall, 39 patients (78 %) had liver cirrhosis and 11 (22 %) had hepatopathy. Ascites was present in 27 patients (54 %). According to Child–Pugh classification, five patients (10 %) were class A, 27 (54 %) class B, and 18 (36 %) class C. The ultrasonographic assessment showed F4 fibrosis in 39 patients (78 %), F3 in six (12 %), F2 in four (8 %), and F1 in one patient (2 %).

**Table 1.** Baseline demographic and hepatic characteristics.

| Characteristic | Category | n | % |
|---|---|---|---|
| Sex | Male | 42 | 84 |
| | Female | 8 | 16 |
| Area of residence | Urban | 16 | 32 |
| | Rural | 34 | 68 |
| Age group | ≤50 years | 9 | 18 |
| | 51–60 years | 14 | 28 |
| | 61–70 years | 17 | 34 |
| | >70 years | 10 | 20 |
| Main hepatic diagnosis | Liver cirrhosis | 39 | 78 |
| | Hepatopathy | 11 | 22 |
| Ascites | Present | 27 | 54 |
| | Absent | 23 | 46 |
| Child–Pugh class | A | 5 | 10 |
| | B | 27 | 54 |
| | C | 18 | 36 |
| Ultrasonographic fibrosis | F1 | 1 | 2 |
| | F2 | 4 | 8 |
| | F3 | 6 | 12 |
| | F4 | 39 | 78 |

### *3.2. Distribution of Psychiatric and Neuropsychiatric Phenotypes*

Hepatic encephalopathy was the most frequent neuropsychiatric manifestation, occurring in 30 patients (60%). Anxiety-depressive manifestations were recorded in 27 patients (54%), insomnia in 25 (50%), alcohol-related psychosis in 11 (22%), and delirium tremens in eight patients (16%) as summarized in Table 2.

**Table 2.** Prevalence of psychiatric and neuropsychiatric phenotypes.

| Phenotype | Present, n | Present, % | Absent, n | Absent, % |
|---|---|---|---|---|
| Hepatic encephalopathy | 30 | 60 | 20 | 40 |
| Anxiety-depressive manifestations | 27 | 54 | 23 | 46 |
| Delirium tremens | 8 | 16 | 42 | 84 |
| Alcohol-related psychosis | 11 | 22 | 39 | 78 |
| Insomnia | 25 | 50 | 25 | 50 |

### *3.3. Psychiatric Phenotypes According to Sex, Area of Residence, and Age*

No statistically significant sex-related or area of residence differences were identified for any phenotype. Age was significantly associated with hepatic encephalopathy ($\chi^2$ = 10.350, $p$ = 0.016), with higher frequencies observed in patients aged 51–60 years (78.6%) and 61–70 years (76.5%), as detailed in Table 2 and Table 3.

**Table 3.** Distribution of psychiatric/neuropsychiatric phenotypes by demographic characteristics.

| Phenotype | Male % | Female % | *p* (Sex) | Urban % | Rural % | *p* (Residence) | ≤50 % | 51–60 % | 61–70 % | >70 % | *p* (Age) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hepatic encephalopathy | 57.1 | 75 | 0.450 | 56.3 | 61.8 | 0.710 | 33.3 | 78.6 | 76.5 | 30 | 0.016 |
| Anxiety-depressive manifestations | 52.4 | 62.5 | 0.711 | 43.8 | 58.8 | 0.318 | 66.7 | 50 | 41.2 | 70 | 0.419 |
| Delirium tremens | 16.7 | 12.5 | 1.000 | 12.5 | 17.6 | 1.000 | 0 | 21.4 | 17.6 | 20 | 0.537 |
| Alcohol-related psychosis | 26.2 | 0.0 | 0.174 | 18.8 | 23.5 | 1.000 | 11.1 | 14.3 | 23.5 | 40 | 0.389 |
| Insomnia | 54.8 | 25 | 0.247 | 62.5 | 44.1 | 0.225 | 55.6 | 50 | 35.3 | 70 | 0.364 |

### *3.4. Overall Laboratory Profile*

Mean serum IgA was 6.23 ± 2.56 g/L and IgG was 15.58 ± 4.29 g/L. Mean GGT was 358.14 U/L, AST 298.77 U/L, ALT 106.90 U/L, albumin 2.88 g/dL. Total bilirubin 3.80 mg/dL, direct bilirubin 2.35 mg/dL, INR 1.76, hemoglobin 10.79 g/dL, MCV 91.27 fL, and platelet count 174.30 × $10^3$/μL as summarized in Table 4.

**Table 4.** Overall biochemical and hematological profile.

| Biomarker | n | Mean ± SD | Median (Q1–Q3) |
|---|---|---|---|
| IgA g/L) | 50 | 6.23 ± 2.561 | 6.02 (4.33–8.50) |
| IgG (g/L) | 50 | 15.58 ± 4.290 | 16.80 (12.61–18.48) |
| GGT (U/L) | 50 | 358.14 ± 581.484 | 227.70 (65.88–338.47) |
| TGO (U/L) | 50 | 298.77 ± 1046.892 | 56.79 (32.02–135.85) |
| TGP (U/L) | 50 | 106.90 ± 302.786 | 40.25 (19.90–79.21) |
| Albumin (g/dL) | 49 | 2.88 ± 0.523 | 2.90 (2.60–3.20) |
| Total bilirubin (mg/dL) | 50 | 3.80 ± 5.459 | 2.16 (1.44–3.45) |
| Direct bilirubin (mg/dL) | 50 | 2.35 ± 3.686 | 1.29 (0.65–2.21) |

| | | | |
|---|---|---|---|
| INR | 50 | 1.76 ± 0.804 | 1.50 (1.27–1.91) |
| Hemoglobin (g/dL) | 50 | 10.79 ± 2.388 | 10.40 (8.85–12.80) |
| MCV (fL) | 50 | 91.27 ± 14.626 | 93.40 (89.25–97.73) |
| Platelets ($10^3$/μL) | 50 | 174.30 ± 100.992 | 158.50 (87.50–257.25) |

### *3.5. Biochemical Profiles Across Psychiatric and Neuropsychiatric Phenotypes*

The detailed biomarker comparisons across psychiatric phenotypes are summarized in Table 5 and Table 6.

Patients with HE had significantly higher IgA (7.09 ± 2.33 vs. 4.94 ± 2.39 g/L; U = 149.0, $p = 0.003$) and IgG (16.83 ± 3.68 vs. 13.72 ± 4.55 g/L; U = 189.5, $p = 0.029$) and lower hemoglobin (10.20 ± 1.98 vs. 11.66 ± 2.71 g/dL; U = 186.5, $p = 0.025$).

Delirium tremens was associated with lower hemoglobin (9.40 ± 2.15 vs. 11.05 ± 2.36 g/dL; $p = 0.039$). Alcohol-related psychosis was associated with lower albumin (2.61 ± 0.36 vs. 2.96 ± 0.54 g/dL; $p = 0.021$) and lower hemoglobin (9.67 ± 2.74 vs. 11.10 ± 2.22 g/dL; $p = 0.026$). Insomnia was associated with significantly higher GGT levels (436.12 ± 603.37 vs. 280.16 ± 560.02 U/L; $p = 0.028$).

**Table 5.** Detailed biomarker comparison: Hepatic encephalopathy.

| Biomarker | Absent n | Absent Mean ± SD | Absent Median (Q1–Q3) | Present n | Present Mean ± SD | Present Median (Q1–Q3) | U | *p* | Effect Size (r) |
|---|---|---|---|---|---|---|---|---|---|
| IgA (g/L) | 20 | 4.94 ± 2.392 | 4.37 (2.87–6.54) | 30 | 7.09 ± 2.327 | 7.15 (5.15–8.92) | 149.000 | 0.003 | −0.423 |
| IgG (g/L) | 20 | 13.72 ± 4.548 | 14.44 (8.72–17.81) | 30 | 16.83 ± 3.679 | 16.96 (14.79–18.62) | 189.500 | 0.029 | −0.309 |
| GGT (U/L) | 20 | 414.96 ± 661.934 | 233.52 (71.12–373.60) | 30 | 320.26 ± 529.655 | 195.25 (56.83–338.38) | 276.500 | 0.642 | −0.066 |
| TGO (U/L) | 20 | 98.04 ± 141.552 | 42.42 (29.72–113.78) | 30 | 432.59 ± 1338.803 | 74.38 (42.06–154.14) | 205.500 | 0.061 | −0.265 |
| TGP (U/L) | 20 | 52.11 ± 49.588 | 31.29 (17.98–78.56) | 30 | 143.43 ± 387.098 | 42.60 (20.51–79.36) | 269.500 | 0.546 | −0.085 |
| Albumin (g/dL) | 20 | 2.95 ± 0.644 | 2.95 (2.53–3.39) | 29 | 2.84 ± 0.427 | 2.90 (2.62–3.06) | 267.000 | 0.639 | −0.066 |
| Total Bilirubin (mg/dL) | 20 | 3.00 ± 5.463 | 1.82 (0.82–2.50) | 30 | 4.33 ± 5.484 | 2.32 (1.66–4.63) | 206.500 | 0.064 | −0.262 |
| Direct Bilirubin (mg/dL) | 20 | 1.88 ± 3.606 | 0.79 (0.43–1.84) | 30 | 2.66 ± 3.766 | 1.34 (1.01–2.31) | 219.000 | 0.109 | −0.227 |
| INR | 20 | 1.51 ± 0.516 | 1.41 (1.15–1.80) | 30 | 1.93 ± 0.920 | 1.60 (1.45–1.96) | 208.500 | 0.070 | −0.256 |
| Hemoglobin (g/dL) | 20 | 11.66 ± 2.713 | 11.90 (10.03–13.48) | 30 | 10.20 ± 1.983 | 9.95 (8.38–11.83) | 186.500 | 0.025 | −0.318 |
| MCV (fL) | 20 | 89.85 ± 18.889 | 92.95 (89.30–101.20) | 30 | 92.22 ± 11.197 | 93.60 (89.18–96.50) | 294.000 | 0.905 | −0.017 |
| Platelets ($10^3$/μL) | 20 | 174.70 ± 97.217 | 157.00 (84.50–259.75) | 30 | 174.03 ± 105.078 | 160.00 (87.50–250.25) | 296.000 | 0.937 | −0.011 |

**Table 6.** Detailed biomarker comparison: Anxiety-depressive manifestations.

| Biomarker | Absent n | Absent Mean ± SD | Absent Median (Q1–Q3) | Present n | Present Mean ± SD | Present Median (Q1–Q3) | U | *p* | Effect Size (r) |
|---|---|---|---|---|---|---|---|---|---|
| IgA (g/L) | 23 | 6.21 ± 2.473 | 6.55 (4.40–8.33) | 27 | 6.25 ± 2.681 | 5.55 (4.30–8.75) | 308.000 | 0.961 | −0.007 |
| IgG (g/L) | 23 | 15.40 ± 4.268 | 15.92 (11.88–18.55) | 27 | 15.74 ± 4.382 | 17.13 (12.85–18.45) | 281.500 | 0.572 | −0.080 |
| GGT (U/L) | 23 | 285.48 ± 280.746 | 240.30 (59.93–420.50) | 27 | 420.04 ± 749.594 | 169.04 (67.86–270.75) | 286.000 | 0.633 | −0.067 |
| TGO (U/L) | 23 | 505.77 ± 1521.388 | 56.56 (31.42–146.79) | 27 | 122.44 ± 191.806 | 62.54 (33.56–133.32) | 301.000 | 0.853 | −0.026 |
| TGP (U/L) | 23 | 162.85 ± 438.521 | 43.18 (20.70–85.17) | 27 | 59.24 ± 70.257 | 35.73 (17.00–72.29) | 256.000 | 0.289 | −0.150 |
| Albumin (g/dL) | 22 | 2.93 ± 0.499 | 2.90 (2.60–3.10) | 27 | 2.85 ± 0.548 | 2.90 (2.60–3.20) | 277.500 | 0.695 | −0.056 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Total Bilirubin (mg/dL) | 23 | 3.13 ± 4.133 | 2.14 (1.27–2.70) | 27 | 4.37 ± 6.401 | 2.18 (1.50–3.61) | 287.000 | 0.647 | −0.065 |
| Direct Bilirubin (mg/dL) | 23 | 1.95 ± 2.967 | 1.18 (0.66–2.20) | 27 | 2.68 ± 4.231 | 1.35 (0.57–2.23) | 304.500 | 0.907 | −0.017 |
| INR | 23 | 1.83 ± 0.985 | 1.50 (1.17–1.80) | 27 | 1.70 ± 0.622 | 1.49 (1.27–1.92) | 309.000 | 0.977 | −0.004 |
| Hemoglobin (g/dL) | 23 | 11.13 ± 2.348 | 11.30 (9.40–12.80) | 27 | 10.49 ± 2.425 | 10.20 (8.60–12.80) | 270.500 | 0.436 | −0.110 |
| MCV (fL) | 23 | 92.55 ± 11.425 | 93.40 (90.20–95.90) | 27 | 90.19 ± 17.031 | 91.60 (88.80–98.10) | 292.000 | 0.719 | −0.051 |
| Platelets ($10^3$/μL) | 23 | 183.65 ± 108.738 | 179.00 (89.00–275.00) | 27 | 166.33 ± 95.257 | 150.00 (83.00–229.00) | 282.500 | 0.586 | −0.077 |

Further potentiak biomarker comparison for delirium tremens, alcohol-related psychosis and insomnia are presented in Table 7, 8 ,9.

**Table 7.** Detailed biomarker comparison: Delirium tremens.

| Biomarker | Absent n | Absent Mean ± SD | Absent Median (Q1–Q3) | Present n | Present Mean ± SD | Present Median (Q1–Q3) | U | *p* | Effect Size (r) |
|---|---|---|---|---|---|---|---|---|---|
| IgA (g/L) | 42 | 6.07 ± 2.619 | 5.53 (4.30–8.37) | 8 | 7.08 ± 2.180 | 7.44 (4.86–9.16) | 130.000 | 0.315 | −0.142 |
| IgG (g/L) | 42 | 15.30 ± 4.445 | 16.53 (11.84–18.48) | 8 | 17.07 ± 3.174 | 18.11 (14.62–18.49) | 132.500 | 0.347 | −0.133 |
| GGT (U/L) | 42 | 314.03 ± 493.444 | 227.70 (53.90–320.82) | 8 | 589.72 ± 931.538 | 213.15 (75.66–765.71) | 135.500 | 0.390 | −0.122 |
| TGO (U/L) | 42 | 148.94 ± 312.746 | 56.79 (31.38–121.53) | 8 | 1085.39 ± 2501.427 | 93.67 (42.03–797.52) | 131.500 | 0.334 | −0.137 |
| TGP (U/L) | 42 | 64.40 ± 80.585 | 40.25 (19.90–79.21) | 8 | 330.01 ± 732.117 | 41.64 (13.80–256.09) | 163.500 | 0.905 | −0.017 |
| Albumin (g/dL) | 41 | 2.91 ± 0.530 | 2.90 (2.62–3.20) | 8 | 2.75 ± 0.497 | 2.70 (2.42–2.87) | 109.500 | 0.140 | −0.209 |
| Total Bilirubin (mg/dL) | 42 | 3.88 ± 5.903 | 2.12 (1.19–3.42) | 8 | 3.37 ± 2.061 | 2.30 (1.90–4.79) | 125.000 | 0.255 | −0.161 |
| Direct Bilirubin (mg/dL) | 42 | 2.48 ± 4.008 | 1.22 (0.59–2.24) | 8 | 1.64 ± 0.566 | 1.49 (1.12–2.13) | 128.000 | 0.290 | −0.150 |
| INR | 42 | 1.71 ± 0.789 | 1.48 (1.24–1.86) | 8 | 2.02 ± 0.883 | 1.84 (1.62–2.02) | 104.000 | 0.090 | −0.240 |
| Hemoglobin (g/dL) | 42 | 11.05 ± 2.361 | 10.95 (9.40–12.80) | 8 | 9.40 ± 2.154 | 8.35 (7.83–11.28) | 90.000 | 0.039 | −0.292 |
| MCV (fL) | 42 | 91.97 ± 14.426 | 93.85 (90.13–97.73) | 8 | 87.64 ± 16.140 | 85.50 (78.63–104.45) | 107.000 | 0.106 | −0.228 |
| Platelets ($10^3$/μL) | 42 | 179.57 ± 102.508 | 158.50 (93.50–261.50) | 8 | 146.61 ± 93.849 | 132.00 (63.50–219.23) | 137.500 | 0.200 | −0.114 |

**Table 8.** Detailed biomarker comparison: Alcohol-related psychosis.

| Biomarker | Absent n | Absent Mean ± SD | Absent Median (Q1–Q3) | Present n | Present Mean ± SD | Present Median (Q1–Q3) | U | *p* | Effect Size (r) |
|---|---|---|---|---|---|---|---|---|---|
| IgA (g/L) | 39 | 5.96 ± 2.602 | 5.45 (4.22–8.36) | 11 | 7.18 ± 2.266 | 6.55 (5.50–9.30) | 152.000 | 0.143 | −0.207 |
| IgG (g/L) | 39 | 15.20 ± 4.491 | 16.80 (11.70–18.45) | 11 | 16.94 ± 3.304 | 18.28 (14.01–18.55) | 177.500 | 0.386 | −0.123 |
| GGT (U/L) | 39 | 397.11 ± 642.210 | 239.22 (67.86–391.16) | 11 | 219.97 ± 250.275 | 140.08 (59.93–279.12) | 189.500 | 0.558 | −0.083 |
| TGO (U/L) | 39 | 173.18 ± 351.442 | 57.01 (31.42–117.60) | 11 | 744.04 ± 2149.737 | 56.56 (38.23–166.29) | 190.500 | 0.574 | −0.079 |
| TGP (U/L) | 39 | 69.07 ± 90.540 | 40.30 (18.08–77.42) | 11 | 241.01 ± 626.667 | 40.09 (20.50–94.39) | 213.500 | 0.981 | −0.003 |
| Albumin (g/dL) | 38 | 2.96 ± 0.539 | 2.91 (2.62–3.24) | 11 | 2.61 ± 0.362 | 2.70 (2.39–2.89) | 113.000 | 0.021 | −0.326 |
| Total Bilirubin (mg/dL) | 39 | 3.57 ± 5.072 | 2.12 (1.27–3.43) | 11 | 4.62 ± 6.879 | 2.26 (1.52–4.55) | 196.000 | 0.665 | −0.061 |
| Direct Bilirubin (mg/dL) | 39 | 2.26 ± 3.496 | 1.25 (0.59–2.27) | 11 | 2.65 ± 4.471 | 1.46 (1.01–1.92) | 193.000 | 0.615 | −0.071 |
| INR | 39 | 1.73 ± 0.781 | 1.48 (1.27–1.84) | 11 | 1.88 ± 0.908 | 1.63 (1.18–2.06) | 186.500 | 0.512 | −0.093 |
| Hemoglobin (g/dL) | 39 | 11.10 ± 2.218 | 11.20 (9.70–12.80) | 11 | 9.67 ± 2.738 | 8.60 (7.80–11.80) | 119.500 | 0.026 | −0.315 |
| MCV (fL) | 39 | 91.84 ± 15.011 | 93.90 (89.90–98.10) | 11 | 89.25 ± 13.646 | 89.30 (82.00–95.50) | 151.500 | 0.140 | −0.209 |
| Platelets ($10^3$/μL) | 39 | 179.64 ± 104.940 | 157.00 (97.00–263.00) | 11 | 155.35 ± 87.318 | 163.00 (83.00–229.00) | 191.500 | 0.590 | −0.076 |

**Table 9.** Detailed biomarker comparison: Insomnia.

| Biomarker | Absent n | Absent Mean ± SD | Absent Median (Q1–Q3) | Present n | Present Mean ± SD | Present Median (Q1–Q3) | U | *p* | Effect Size (r) |
|---|---|---|---|---|---|---|---|---|---|
| IgA (g/L) | 25 | 6.53 ± 2.691 | 7.09 (4.58–8.63) | 25 | 5.93 ± 2.441 | 5.11 (4.32–8.54) | 257.000 | 0.281 | −0.152 |
| IgG (g/L) | 25 | 16.27 ± 3.894 | 16.81 (15.39–18.37) | 25 | 14.89 ± 4.628 | 14.53 (11.53–18.56) | 268.000 | 0.388 | −0.122 |
| GGT (U/L) | 25 | 280.16 ± 560.017 | 84.59 (43.80–263.49) | 25 | 436.12 ± 603.366 | 250.35 (151.40–405.83) | 199.500 | 0.028 | −0.310 |
| TGO (U/L) | 25 | 487.28 ± 1466.729 | 52.87 (31.82–137.45) | 25 | 110.25 ± 110.912 | 92.40 (32.28–138.37) | 293.500 | 0.712 | −0.052 |
| TGP (U/L) | 25 | 157.37 ± 422.963 | 40.30 (18.02–86.20) | 25 | 56.43 ± 54.536 | 40.09 (20.51–72.23) | 309.500 | 0.954 | −0.008 |
| Albumin (g/dL) | 24 | 2.96 ± 0.515 | 2.90 (2.67–3.17) | 25 | 2.81 ± 0.531 | 2.88 (2.35–3.28) | 257.000 | 0.389 | −0.122 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Total Bilirubin total (mg/dL) | 25 | 3.59 ± 4.895 | 2.18 (1.60–3.07) | 25 | 4.01 ± 6.066 | 2.12 (1.16–3.72) | 287.500 | 0.628 | −0.069 |
| Direct Bilirubin (mg/dL) | 25 | 2.26 ± 3.230 | 1.27 (0.88–2.29) | 25 | 2.43 ± 4.158 | 1.31 (0.55–2.06) | 286.500 | 0.614 | −0.071 |
| INR | 25 | 1.86 ± 0.879 | 1.49 (1.40–2.10) | 25 | 1.66 ± 0.725 | 1.50 (1.22–1.89) | 285.000 | 0.594 | −0.075 |
| Hemoglobin (g/dL) | 25 | 11.23 ± 2.182 | 11.80 (9.40–12.80) | 25 | 10.34 ± 2.544 | 10.10 (7.95–12.30) | 246.500 | 0.200 | −0.181 |
| MCV (fL) | 25 | 93.74 ± 15.043 | 95.10 (90.40–98.90) | 25 | 88.81 ± 14.066 | 91.00 (82.10–97.00) | 231.500 | 0.116 | −0.222 |
| Platelets ($10^3$/μL) | 25 | 160.04 ± 95.143 | 137.00 (76.50–244.50) | 25 | 188.56 ± 106.527 | 163.00 (101.50–283.00) | 265.000 | 0.357 | −0.130 |

### *3.6. Multivariable Analysis of Factors Associated with Hepatic Encephalopathy*

The final multivariable binary logistic regression model included age 51–70 years, IgG, and hemoglobin. The model demonstrated good fit (Hosmer–Lemeshow $p = 0.621$; Nagelkerke $R^2 = 47.5\%$; AUC = 0.849). The age 51–70 years (OR = 11.882, 95% CI: 2.268–62.244, $p = 0.003$) and higher IgG (OR = 1.288 per g/L, 95% CI: 1.035–1.603, $p = 0.023$) remained independently associated with HE, as detailed in Table 10.

**Table 10.** Final parsimonious logistic regression model for hepatic encephalopathy.

| Predictor | B | *p* | OR | 95% CI for OR |
|---|---|---|---|---|
| Age 51–70 years | 2.475 | 0.003 | 11.882 | 2.268–62.244 |
| IgG | 0.253 | 0.023 | 1.288 | 1.035–1.603 |
| Hemoglobin | −0.324 | 0.063 | 0.723 | 0.514–1.018 |
| Constant | −1.495 | 0.534 | 0.224 | — |

## 4. Discussion

The present study provides a phenotype-oriented clinical and biochemical evaluation of psychiatric and neuropsychiatric comorbidities in hospitalized patients with alcohol-related liver disease (ALD). By examining distinct psychiatric and neuropsychiatric manifestations independently rather than as a uniform entity, our findings highlight a high cumulative burden of neuropsychiatric morbidity: hepatic encephalopathy (HE, 60.0%), anxiety-depressive manifestations (54.0%), insomnia (50.0%), alcohol-related psychosis (22.0%), and delirium tremens (16.0%). The primary biological findings include significantly elevated serum IgA and IgG concentrations among patients with HE, alongside distinct hematological and hepatic alterations across other clinical phenotypes. In multivariable binary logistic regression, an age between 51 and 70 years and higher serum IgG concentrations remained independently associated with the presence of HE.

First and foremost, the elevation of serum IgA and IgG concentrations observed in patients with HE aligns with the pathophysiological framework of gut–liver–brain axis disruption and systemic immune dysregulation in advanced ALD. In chronic alcohol exposure, intestinal hyperpermeability ("leaky gut") and dysbiosis promote the translocation of gut-derived bacterial products and lipopolysaccharides into the portal circulation. Chronic mucosal antigen exposure stimulates localized B-cell class switching to IgA, while persistent portal endotoxemia and impaired hepatic reticuloendothelial clearance drive systemic hypergammaglobulinemia (elevated IgG) [15,16]. Serum IgA and IgG concentrations primarily reflect the clinical severity of underlying liver dysfunction, portal hypertension, and impaired reticuloendothelial bacterial clearing capacity. Concurrently, systemic immune activation and circulating inflammatory mediators can compromise blood–brain barrier integrity, triggering neuroinflammation, microglial activation, and astroglial swelling that exacerbate cognitive and behavioral impairment in HE. Nevertheless, because direct plasma ammonia levels and circulating pro-inflammatory cytokines were not quantified in this study, the exact biological linkage between humoral immune markers and neurocognitive impairment remains exploratory.

The high prevalence of affective and sleep disorders in our cohort further underscores the complex interplay between medical and psychiatric morbidity in chronic liver disease. Anxiety-depressive manifestations (54.0%) and insomnia (50.0%) were among the most frequent clinical phenotypes. These findings mirror recent population-level epidemiological studies demonstrating a rising prevalence of major depressive disorder and

anxiety disorders among hospitalized ALD patients. In our subgroup analyses, insomnia was significantly associated with elevated serum GGT levels, a marker reflecting both recent heavy alcohol intake and advanced hepatic oxidative stress. Furthermore, depressive and anxiety symptoms in patients with liver disease may exacerbate non-adherence to medical therapy, impair self-care, and diminish overall quality of life.

Severe withdrawal states and psychotic disorders represented less frequent but clinically severe phenotypes. Delirium tremens (16.0%) and alcohol-related psychosis (22.0%) were both significantly characterized by lower mean hemoglobin levels, while alcohol-related psychosis was additionally associated with significantly lower serum albumin concentrations. Anemia and hypoalbuminemia are established markers of advanced hepatic decompensation, systemic catabolism, and severe nutritional depletion. The presence of underlying advanced liver injury in patients presenting with severe withdrawal states or alcohol-related hallucinosis complicates clinical management, increases susceptibility to infectious complications, and prolongs hospitalization.

A critical methodological limitation of the multivariable logistic regression model for hepatic encephalopathy is the potential for residual confounding. Owing to sample size constraints (n = 50, with 30 HE cases), established measures of liver disease severity—such as Child-Pugh score/class, MELD score, or the presence of ascites—could not be entered simultaneously into the regression model alongside IgG without inducing severe overfitting. Consequently, whether elevated serum IgG acts as a direct pathogenic contributor to neuroinflammation or functions primarily as a surrogate marker for advanced hepatic dysfunction cannot be definitively resolved from these data. Moreover, the wide 95% confidence interval observed for age 51–70 years (OR = 11.882, 95% CI: 2.268–62.244) and the small cell sizes for subgroup outcomes (e.g., delirium tremens, n = 8) reflect substantial statistical uncertainty, requiring cautious interpretation.

Finally, several additional limitations inherent to the study design must be recognized. First, the single-center cross-sectional design precludes any causal or temporal inferences regarding the relationship between biochemical markers, liver disease progression, and neuropsychiatric phenotypes. Second, neuropsychiatric manifestations were identified through clinical evaluation during admission without the use of structured, validated psychometric rating scales (e.g., HAM-D, HAM-A, or PHES). Third, the relatively small sample size (n = 50) limited statistical power, particularly for female patients (n = 8) and urban residents (n = 16), rendering subgroup comparisons by sex and residence inconclusive. Future multicenter prospective studies incorporating standardized psychometric tools, longitudinal follow-up, and comprehensive immune profiling (including inflammatory cytokines and microflora dynamics) are warranted to confirm and expand upon these preliminary findings.

Fourth, anthropometric parameters such as body mass index (BMI) and nutritional biomarkers—most notably serum thiamine (vitamin B1) levels—were not systematically recorded or quantified. Because malnutrition and thiamine deficiency are prevalent in chronic alcohol use and play a well-established role in neuropsychiatric manifestations such as Wernicke–Korsakoff spectrum disorders, delirium tremens, and cognitive impairment, their absence represents an additional limitation that should be addressed in future studies.

## 5. Conclusions

Psychiatric and neuropsychiatric comorbidities—particularly hepatic encephalopathy, anxiety-depressive manifestations, and insomnia—are prevalent among hospitalized patients with alcohol-related liver disease (ALD), reflecting a substantial clinical burden. In univariate analyses, patients with hepatic encephalopathy exhibited significantly higher serum IgA and IgG concentrations, lower hemoglobin levels, and a higher

frequency in the 51–70 age group. In multivariable analysis, age 51–70 years and higher serum IgG concentrations remained independently associated with hepatic encephalopathy, highlighting the complex interplay between demographic factors and systemic immune dysregulation in ALD.

Other distinct clinical phenotypes demonstrated identifiable biological patterns, including lower hemoglobin in delirium tremens, reduced albumin and hemoglobin in alcohol-related psychosis, and elevated GGT in insomnia. Given the cross-sectional design, lack of standardized psychometric rating scales, and relatively small sample size, these exploratory findings—particularly regarding serum immunoglobulins as potential surrogate markers of disease severity or gut–liver–brain axis dysfunction—warrant prospective validation in larger, multicenter cohorts using validated psychometric tools and longitudinal immune profiling.

**Author Contributions:** Conceptualization, A.M.S. and C.O.; methodology, E.P.D.; software, E.N.; validation, C.O., E.P.D. and L.A.; formal analysis, L.A.; investigation, A.M.S.; resources, E.P.D.; data curation, L.A.; writing—original draft preparation, A.M.S.; writing—review and editing, C.O.; visualization, E.P.D.; supervision, E.P.D.; project administration, A.M.S.; funding acquisition, E.N. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of "Sf.Apostol Andrei" Emergency Clinical County Hospital Galati, Romania, approval no 6627/08 April 2025.

**Informed Consent Statement:** Written informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study are available from the corresponding authors upon reasonable request.

**Acknowledgments:** The authors have reviewed and edited the output and take full responsibility for the content of this publication.

**Conflicts of Interest:** The authors declare no conflicts of interest.

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