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„Zaburzenia poznawcze u pacjentów z chorobą wątroby zależną od alkoholu – ocena przed i po transplantacji wątroby”

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu
w dyscyplinie nauki medyczne

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Spis treści

Wykaz używanych skrótów

Skrót	Polska nazwa	Angielska nazwa
ALD	choroba wątroby związana z alkoholem	Alcohol-Related Liver Disease
AUD	zaburzenie używania alkoholu	Alcohol Use Disorder
HE	encefalopatia wątrobowa	Hepatic Encephalopathy
LT	transplantacja wątroby	Liver Transplantation
ACE-III	Test Addenbrooke'a do oceny funkcji poznawczych III	Addenbrooke's Cognitive Examination III
HCC	rak wątrobowokomórkowy	Hepatocellular Carcinoma
MCI	lekkie zaburzenia poznawcze	Mild Cognitive Impairment
MRI	obrazowanie rezonansem magnetycznym	Magnetic Resonance Imaging
TNF-α	czynnik martwicy nowotworów alfa	Tumor Necrosis Factor alpha
IL-6	interleukina 6	Interleukin-6
IL-1β	interleukina 1 beta	Interleukin-1 beta
MCP1	białko chemotaktyczne monocytów 1	Monocyte Chemotactic Protein 1
HPA	oś podwzgórze–przysadka–nadnercza	Hypothalamic–Pituitary–Adrenal Axis
OR	iloraz szans	Odds Ratio
CI	zaburzenia poznawcze	Cognitive Impairment
DSM-5	Podręcznik diagnostyczny i statystyczny zaburzeń psychicznych, 5. edycja	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
WHO	Światowa Organizacja Zdrowia	World Health Organization
NSDUH	Krajowe badanie używania narkotyków i zdrowia	National Survey on Drug Use and Health
MoCA	Skala ocen funkcji poznawczych Montreal	Montreal Cognitive Assessment
FAB	Skala oceny funkcji czołowych	Frontal Assessment Battery
IQR	rozstęp międzykwartylowy	Interquartile Range
SD	odchylenie standardowe	Standard Deviation
p	wartość p	p-value
n	liczba badanych/uczestników	number of subjects/participants

Streszczenie w języku polskim

Wstęp: Zaburzenia funkcji poznawczych (cognitive impairment, CI) u chorych z marskością wątroby są zwykle postrzegane przez pryzmat encefalopatii wątrobowej. Dotychczasowe badania były dodatkowo prowadzone w grupach chorych o różnych etiologiach niewydolności wątroby, przy użyciu różnych narzędzi. Choroba wątroby związana z alkoholem (ALD) stanowi szczególną populację, w której ryzyko CI może być najwyższe, a mechanizmy zaburzeń – złożone i nie w pełni poznane.

Cel: Celem cyklu badań była ocena skali, dynamiki i potencjalnych mechanizmów zaburzeń poznawczych u pacjentów z ALD poddawanych przeszczepieniu wątroby (LT).

Materiał i metody: W pierwszym badaniu porównano funkcje poznawcze kandydatów do LT z ALD (n = 31) z grupą pacjentów z niewydolnością nerek oczekujących na transplantację (n = 31), stosując kwestionariusz ACE-III.

W drugim badaniu przeprowadzono prospektywną ocenę funkcji poznawczych u pacjentów z ALD przed (n=101) i po LT (n=55), analizując zmiany w poszczególnych domenach neuropsychologicznych ACE-III.

W trzecim badaniu oceniono związki pomiędzy poziomem amoniaku we krwi, wynikami badań MRI mózgu a nasileniem CI w tej samej kohorcie pacjentów a ALD (n-52).

Wyniki: Kandydaci z ALD osiągnęli istotnie gorsze wyniki testu ACE-III niż pacjenci oczekujący na transplantację nerki (średnio 70,9 vs 91,6 pkt w ACE-III), a częstość CI była znacznie wyższa w populacji chorych ze schyłkową niedomogą wątroby o etiologii alkoholowej (90% vs 26%).

W badaniu prospektywnym aż 86% pacjentów z ALD miało CI przed LT, a ponad połowa spełniała kryteria wysokiego ryzyka otępienia. Po transplantacji wątroby (ok. 7 mies. po procedurze) obserwowano poprawę w zakresie pamięci, płynności słownej i funkcjach wzrokowo-przestrzennych, jednak deficyty nie ustępowały całkowicie, a domena językowa nawet uległa pogorszeniu u niektórych chorych.

Analiza potencjalnych mechanizmów wykazała, że ani hiperamonemia, ani zmiany w obrazie MRI mózgowia nie tłumaczą w pełni deficytów poznawczych, co podważa dotychczasowe uproszczone modele patofizjologiczne.

Wnioski: Pacjenci z ALD oczekujący na leczenie przeszczepowe stanowią grupę wysokiego ryzyka zaburzeń poznawczych. Przeszczepienie wątroby prowadzi do częściowej, ale niepełnej poprawy funkcji poznawczych, a część deficytów utrzymuje się lub nasila po operacji. Ani poziom amoniaku we krwi, ani zmiany strukturalne w MRI mózgowia, nie wyjaśniają w pełni patogenezy CI, co wskazuje na wieloczynnikowy charakter zaburzeń. Wyniki badań podkreślają konieczność systematycznej oceny neuropsychologicznej oraz długoterminowego wsparcia poznawczego u pacjentów z ALD zarówno przed, jak i po LT.

Streszczenie w języku angielskim

"Cognitive Impairment in Patients with Alcohol-Related Liver Disease - Assessment Before and After Liver Transplantation"

Abstract

Introduction: Cognitive impairment (CI) in patients with liver cirrhosis is usually considered primarily in the context of hepatic encephalopathy. Previous studies have also been conducted in cohorts with mixed etiologies of liver failure, using various assessment tools. Alcohol-associated liver disease (ALD) represents a distinct population in which the risk of CI may be the highest, and the underlying mechanisms are complex and not fully understood.

Objective: The aim of this research cycle was to evaluate the prevalence, dynamics, and potential mechanisms of cognitive impairment in patients with ALD undergoing liver transplantation (LT).

Materials and methods: In the first study, cognitive function was compared between candidates for LT with ALD (n = 31) and patients with end-stage renal disease awaiting kidney transplantation (n = 31), using the ACE-III questionnaire.

In the second study, a prospective evaluation of cognitive function was performed in patients with ALD before (n = 101) and after LT (n = 55), analyzing changes across specific neuropsychological domains of ACE-III.

In the third study, associations were examined between blood ammonia levels, brain MRI findings, and severity of CI in the same cohort of ALD patients (n = 52).

Results: ALD candidates scored significantly lower on the ACE-III test than kidney transplant candidates (mean 70.9 vs. 91.6 points), and the prevalence of CI was markedly higher in the ALD group (90% vs. 26%).

In the prospective study, 86% of ALD patients had CI before LT, and more than half met criteria for high dementia risk. After transplantation, improvement was observed in memory, verbal fluency, and visuospatial functions; however, deficits did not fully resolve, and language function even deteriorated in some patients.

Analysis of potential mechanisms demonstrated that neither hyperammonemia nor MRI abnormalities fully explained the observed deficits, challenging previously simplified pathophysiological models.

Conclusions: ALD patients awaiting liver transplantation represent a high-risk group for cognitive impairment. LT leads to partial but incomplete cognitive recovery, with some deficits persisting or worsening postoperatively. Neither blood ammonia levels nor structural brain MRI findings fully account for the pathogenesis of CI, indicating a multifactorial etiology. These results emphasize the need for systematic neuropsychological assessment and long-term cognitive support in ALD patients both before and after LT.

Wstęp i uzasadnienie cyklu publikacji

Alkoholowa choroba wątroby (ALD) jest jednym z głównych wskazań do transplantacji wątroby w Europie i Ameryce Północnej, a marskość związana z ALD stanowi rosnące obciążenie kliniczne i społeczne. W tej populacji szczególne znaczenie mają zaburzenia funkcji poznawczych (cognitive impairment, CI), które wpływają na jakość życia, przestrzeganie zaleceń terapeutycznych oraz rokowanie po transplantacji. Tradycyjnie deficyty kognitywne tłumaczono niemal wyłącznie encefalopatią wątrobową i towarzyszącą hiperamonemią, jednak współczesne dane wskazują, że mechanizmy te są znacznie bardziej złożone. Na obraz kliniczny nakłada się neurotoksyczne działanie alkoholu, prowadzące do uszkodzeń kory czołowej, hipokampa i móżdżku oraz zaniku istoty białej. Przewlekła hiperamonemia powoduje obrzęk astrocytów i zaburzenia neurotransmisji, podczas gdy stres oksydacyjny, mechanizmy neurozapalne i niedobory żywieniowe dodatkowo uszkadzają sieci neuronalne

i nasilają degenerację. W efekcie u chorych z ALD obserwuje się szerokie spektrum deficytów, obejmujące uwagę, pamięć roboczą i epizodyczną, funkcje językowe, płynność słowną oraz zdolności wzrokowo-przestrzenne.

Dotychczasowe badania nad CI w marskości wątroby opierały się głównie na grupach heterogennych, obejmujących pacjentów z różnymi etiologiami niewydolności wątroby i badanych przy użyciu odmiennych narzędzi neuropsychologicznych. Utrudniało to jednoznaczną interpretację wyników i ograniczało ich wartość kliniczną. Prezentowany cykl trzech publikacji stanowi pierwszą próbę systematycznej i konsekwentnej oceny problemu w jednorodnej populacji chorych z marskością wątroby zależną od alkoholu. Wykorzystanie dobrze zwalidowanego narzędzia diagnostycznego, jakim jest Addenbrooke's Cognitive Examination III (ACE-III), pozwoliło na rzetelną analizę poszczególnych domen poznawczych w sposób porównywalny pomiędzy kolejnymi etapami badań.

Trzy prace składają się na spójny i logiczny cykl, w którym przeanalizowano kolejno skalę problemu, dynamikę zmian w czasie oraz potencjalne mechanizmy patofizjologiczne. Całość cyklu wnosi istotny i oryginalny wkład do wiedzy o zaburzeniach poznawczych w alkoholowej chorobie wątroby. Wyniki podkreślają konieczność systematycznej oceny neuropsychologicznej zarówno w okresie kwalifikacji, jak i w obserwacji pooperacyjnej oraz wskazują na potrzebę długoterminowego wsparcia kognitywnego tej grupy pacjentów. Przedstawione badania stanowią spójną, metodologicznie rzetelną i klinicznie ważną odpowiedź na dotychczasowe luki w literaturze oraz fundament dla dalszych prac nad mechanizmami i terapią CI w ALD.

Założenia i cel pracy

Prezentowany cykl prac został zaprojektowany w celu kompleksowej oceny problemu CI u pacjentów z alkoholową chorobą wątroby (ALD) w stadium schyłkowej niedomogi narządu - w momencie kwalifikacji do leczenia transplantacją wątroby. Jednorodna kohorta chorych pozwoliła na konsekwentne prześledzenie zagadnienia w trzech wymiarach: skali problemu, dynamiki zmian po transplantacji wątroby (LT) oraz potencjalnych mechanizmów patofizjologicznych.

Celem cyklu badań było:

1. Określenie skali i częstości CI u pacjentów z chorobą wątroby zależną od alkoholu w stadium schyłkowej niedomogi narządu w momencie kwalifikacji do leczenia przeszczepowego, w porównaniu z grupą kontrolną pacjentów nefrologicznych oczekujących na przeszczepienie nerki.

2. Ocena dynamiki funkcji poznawczych przed i po transplantacji wątroby, z uwzględnieniem poszczególnych domen neuropsychologicznych.

3. Weryfikacja roli klasycznego markera, takich jak hiperamonemia oraz zmian w mózgowiu w obrazowaniu rezonansowym mózgu, wiązanych z przewlekłą encefalopatią wątrobową, w wyjaśnianiu przyczyny obserwowanych deficytów poznawczych.

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ORIGINAL ARTICLE

Cognitive impairment in patients awaiting kidney and liver transplantation—A clinically relevant problem?

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Abstract

Introduction: Cognitive impairment (CI) is common in both end-stage kidney disease (ESKD) and alcohol-related liver cirrhosis. The aim of this study was to assess the prevalence and patterns of CI in patients awaiting kidney and liver transplantation, and to identify its determinants.

Methods: In this cross-sectional, prospective study, 31 consecutive patients with ESKD and 31 consecutive patients with alcohol-related liver cirrhosis, all currently on transplant waiting lists, were screened for cognitive decline using the Addenbrooke's Cognitive Examination. Medical history, demographics, and laboratory test results were also collected.

Results: The prevalence of CI among patients with ESKD and alcohol-related liver cirrhosis was 26% and 90%, respectively. In both groups, memory was the most affected cognitive domain, along with verbal fluency in patients with ESKD, and visuospatial abilities in patients with alcoholic cirrhosis. The most statistically significant increase in the prevalence of CI was found in patients with lower educational attainment, in both alcohol-related liver cirrhosis and ESKD populations as well as in older patients with alcoholic cirrhosis. Furthermore, better cognitive functioning in ESKD patients was associated with higher levels of total lymphocyte count and alanine transaminase (ALT), and in alcohol-related liver cirrhosis patients with higher levels of ALT and aspartate transaminase. A nonsignificant trend toward lower memory domain scores was also observed with increasing ammonia levels and increasing severity of liver disease (higher Child–Pugh scores). Finally, suboptimal performance on the screening test was correlated with the severity of liver disease as assessed by the Model for End-Stage Liver Disease Sodium (MELD-Na), but not at the statistically significant level.

Conclusions: The prevalence of CI, especially in patients with alcohol-related liver cirrhosis, is high and can be a significant clinical problem, negatively affecting the transplantation process. Routine screening tests in this group would contribute to

the implementation of appropriate management, such as rehabilitation program or psychosocial treatments and facilitate the provision of specialized health care.

KEYWORDS
cognitive impairment, end-stage kidney disease, end-stage liver disease

1 | INTRODUCTION

Cognitive impairment (CI) among patients with end-stage kidney disease (ESKD) and alcohol-related liver cirrhosis, awaiting transplantation, remains an underestimated but escalating concern worldwide. Pre-existing, unrecognized CI may negatively impact the transplantation process by affecting adherence to clinical and pharmacological recommendations (Smith et al., 2017). It is also associated with poorer patient outcomes, including graft rejection (Golfieri et al., 2019). CI in patients with ESKD may be influenced by many traditional and non-traditional cardiovascular risk factors associated with kidney disease (Pépin et al., 2023). Moreover, patients with alcoholic liver disease, but also with other liver disease etiologies such as chronic hepatitis C infection, nonalcoholic fatty liver disease, and primary biliary cirrhosis exhibit an increased susceptibility to developing CI (Butterworth, 1995; Ruck et al., 2023). Excessive alcohol consumption may cause direct neurotoxic effects on the brain, as well as lead to alcoholic liver disease and the build-up of toxins such as ammonia (Butterworth, 1995). The frontal lobe, the cerebellum, and the limbic system, including the hippocampus, among others, are brain structures particularly vulnerable to alcohol consumption (Oscar-Berman & Marinković, 2007). Furthermore, alcoholic cirrhosis, which is the final stage of alcoholic liver disease, can affect the structure or functioning of the brain, causing brain damage (Harper, 2009).

Solid organ transplantation is the treatment of choice for both ESKD and alcohol-related liver cirrhosis (Rai, 2013). In our previous report, we investigated cognitive function, the impact of immunosuppressive therapy and other kidney disease-related variables on cognitive function in 56 patients after kidney transplantation. We have found that the prevalence of CI in kidney transplant recipients was 30% (Golenia et al., 2023a). As shown in a large, prospective cohort study, the presence of CI in patients with ESKD was associated with a lower chance of being placed on the transplant waiting list, and in patients without diabetes, additionally with increased mortality on the waiting list (Chu et al., 2020). Finally, there are several consistent reports demonstrating the significance of both alcoholic and nonalcoholic fatty liver disease for cognitive decline (Lee et al., 2016; Parikh et al., 2024). Ruck et al. recently published a paper on cognitive dysfunctions in patients with liver disease of various etiologies, indicating that cognitive problems are common in patients with liver disease and are independent of hepatic encephalopathy (Ruck et al., 2023). The prevalence of CI in patients after liver transplantation for liver disease of mixed etiology ranged from 0% to 36% (Siddiqui et al., 2023).

In the present study, we assessed the prevalence of CI in patients with ESKD and alcohol-related liver cirrhosis who were placed on the transplant waiting list. Due to the different pathological mechanisms of alcoholic and nonalcoholic liver disease, we decided to include only patients with alcoholic liver disease in the study. We also differentiated patterns of cognitive dysfunction between the two groups.

2 | MATERIALS AND METHODS

Consecutive patients with ESKD and alcohol-related liver cirrhosis, listed for transplantation, were screened for CI using Addenbrooke's Cognitive Examination (ACE) between January 16, 2023 and May 30, 2023. The protocol for the study was approved by the Bioethics Committee of the Medical University of Warsaw (approval number KB/81/2022). All patients received detailed information regarding the study and researchers obtained written informed consent from every study participant. The research was compliant with the ethical guidelines of the World Medical Association Declaration of Helsinki.

3 | ESKD PATIENTS' RECRUITMENT

Patients were included in the study if they were 18 years of age or older, spoke Polish, had ESKD, were on ambulatory hemodialysis or peritoneal dialysis, and met the hospital's protocol qualifications for kidney transplantation. The following exclusion criteria were used: symptoms of an infectious disease in the previous 8 weeks, and using hypnotics (including benzodiazepines and z-drugs). Past medical history and laboratory test results were obtained from hospital records.

4 | ALCOHOL-RELATED LIVER CIRRHOSIS PATIENTS' RECRUITMENT

Patients were included in the study if they were 18 years of age or older, spoke Polish, had alcohol-related liver cirrhosis (confirmed by radiological imaging and liver biopsy) with features of chronic liver insufficiency, and met the hospital's protocol qualifications for liver transplantation (i.e., no contraindications to this form of therapy were found). Patients were excluded from the study if they had: any infections in the previous 8 weeks or were regularly taking hypnotics (including benzodiazepines and z-drugs). The stage of liver

failure was determined using the Child–Pugh and Model for End-Stage Liver Disease-Sodium (MELD-Na) scores. Past medical history and laboratory test results were obtained from hospital records.

The biochemical parameters were selected on the basis of previously published studies showing their possible association with CI (Gao et al., 2024; Li et al., 2022; Pépin et al., 2023).

5 | COGNITIVE FUNCTIONS' ASSESSMENT

The ACE-III screening test was used to evaluate CI. This test assesses five main cognitive domains, that is, attention, verbal fluency, memory, language, and visuospatial abilities with a score ranging from 0 to 100 points, and takes 15–20 min to complete. Patients were assessed in the morning (between 7:30 a.m. and 11:00 a.m.), in a separate room, in silence, during a scheduled visit to the transplant clinic by one of two researchers. For the diagnosis of mild cognitive impairment (MCI), the range was 88–82 points, and for suspected dementia ≤81 points. At a threshold of 81, the sensitivity for detecting of suspected dementia was 84% and the specificity was 86% (Kaczmarek et al., 2022). The advantages of the ACE-III test, compared to other cognitive screening tests, lie primarily in: (i) its specificity and sensitivity in CI diagnosis, (ii) its feasibility for administration by doctors and other health care professionals, (iii) the fact that it has been verified using standard neuropsychological tests, (iv) the availability of a validated Polish version, provided at no cost. However, the Polish version of the ACE-III test for assessing cognitive functions has not been validated for both patients with ESKD and alcohol-related liver cirrhosis. Nonetheless, it is a validated screening tool assessing global cognitive functioning of elderly people in the general Polish population (Kaczmarek et al., 2022).

6 | STATISTICAL ANALYSIS

Statistical analysis of the data was performed using IBM SPSS Statistics 26 software. In addition to determining the basic descriptive statistics of the datasets, histograms of the frequencies of test scores in different groups were determined. Besides, receiver operating characteristics (ROC) curves and associated area under the curve (AUC) values were determined to characterize the binary classifier to assess normal group membership based on various parameters collected to characterize patients. A ROC curve is generated by running a logistic regression analysis (Swets, 1996) on a dataset. In the case presented here, binary logistic regression is used to diagnose diseases by assessing the presence or absence of CI based on a patient's test results. There is one binary dependent variable, coded by an indicator variable, where the two values are labeled "0" and "1" (non-CI and CI), while the independent variable is a continuous variable (test score or diagnostic parameter value). To quantify the basic classification ability of each parameter included as an independent variable, the AUC is calculated. The Student's *t*-test was used to assess statistical significance when comparing the means of two independent groups.

7 | RESULTS

7.1 | Patients characteristics

The study included 31 consecutive patients with ESKD and 31 consecutive patients with alcohol-related liver cirrhosis, awaiting transplantation. The demographic and clinical characteristics of the study groups are summarized in Table 1. The age distribution was similar in both groups, but in terms of gender distribution, the majority of the alcoholic cirrhosis group were male (77.4%). The mean age for ESKD and alcoholic cirrhosis was 49.94 ± 16.02 years and 55.39 ± 10.48 years, respectively. Furthermore, patients with alcoholic cirrhosis had significantly fewer years of formal schooling than ESKD patients (11.74 ± 4.13 years vs. 15.56 ± 3.76 years, $p > .001$). The mean duration of dialysis in patients with ESKD was 43.45 ± 69.88 months, and patients were on both peritoneal dialysis and hemodialysis (29% vs. 31%).

7.2 | ACE-III test results

The ACE-III test scores were significantly higher in patients with ESKD than in patients with alcoholic cirrhosis (91.58 ± 6.12 vs. 70.9 ± 14.16; $p = .001$, shown in Figure 1). In the group of ESKD patients, the prevalence of CI was 26%, whereas in the group of patients with alcoholic cirrhosis it amounted to 90%. All cognitive domains in patients with alcoholic cirrhosis were significantly impaired as compared to ESKD patients ($p > .001$; Figure 1). The most impaired cognitive domain in both groups was memory, and additionally verbal fluency in patients with ESKD, and visuospatial abilities in patients with alcoholic cirrhosis, as shown in the histograms ($p > .001$, Figure 1).

7.3 | Factors associated with ACE-III scores

The effect of parameter values on their predictive accuracy for binary classification into CI and non-CI groups was examined. Figure 2 shows ROC curves plotted for age, years of education as well as the results for each domain. With the exception of the attention subdomain and age in the ESKD group, all parameters showed the highest sensitivity and specificity for identifying patients without CI (area under ROC curve AUC at least 0.7; Table 2). In addition, the ROC curves were also plotted for blood test parameters such as aspartate aminotransferase (AST), alanine transaminase (ALT), AST/ALT, gamma-glutamyl transferase (GGTP), total lymphocyte count (TLC), creatinine levels and creatinine clearance (eGFR), hemoglobin (Hgb) levels, thyroid-stimulating hormone (TSH), fasting glucose levels, as well as sodium and potassium levels (Figure 3). In the ESKD group, ALT and TLC (maximum values of AUC for ALT was 0.834 and for TLC was 0.698) had the highest sensitivity and specificity for identifying patients without CI, while in the group with alcoholic cirrhosis, AST (AUC = 0.964) and ALT levels (AUC = 0.940) had the best predictive accuracy (Table 3).

TABLE 1 Demographic characteristics, Addenbrooke's Cognitive Examination-III (ACE-III) test results, and blood test results of the study groups.

	Kidney			Liver		
	CI (mean ± SD)	Non-CI (mean ± SD)	*p*	CI (mean ± SD)	Non-CI (mean ± SD)	*p*
Age, years	48.63 ± 11.08	46.91 ± 16.78	.038	57.36 ± 9.59	46.33 ± 6.42	.074
Years of education	12.88 ± 2.1	15.83 ± 2.39	.005	11.32 ± 2.11	14.67 ± 4.04	.287
Lymphocytes (10^3/μL)	1.18 ± 0.37	1.69 ± 0.87	.031	1.28 ± 0.74	0.92 ± 0.25	.110
Hemoglobin (g/dL)	10.48 ± 1.38	11 ± 1.36	.364	11.04 ± 1.58	11.77 ± 2.35	.648
AST (U/L)	19.50 ± 7.91	21.39 ± 8.42	.577	54.50 ± 29.49	126.67 ± 14.15	.002
ALT (U/L)	12.75 ± 4.7	29.43 ± 23.17	.003	36.93 ± 22.69	67.33 ± 21.5	.121
AST/ALT ratio	1.58 ± 0.49	0.91 ± 0.37	.005	1.57 ± 0.54	2.07 ± 0.93	.452
GGTP (U/L)	38.63 ± 43	30.87 ± 19.67	.636	105.18 ± 126.47	109.33 ± 40.77	.905
Creatinine (mg/dL)	8.79 ± 3.45	9.15 ± 2.64	.796	1.085 ± 0.41	0.92 ± 0.14	.194
eGFR (mL/min/1.73 m^2)	7.12 ± 5.11	5.91 ± 2.83	.540	76.64 ± 26.64	91.33 ± 27.79	.461
Sodium (mmol/L)	139.08 ± 5.04	137.3 ± 3.26	.378	132.44 ± 6.57	132.70 ± 1.67	.871
Potassium (mmol/L)	4.99 ± 1.08	4.65 ± 0.76	.425	4.6 ± 0.7	4.32 ± 0.82	.624
TSH (uIU/mL)	2.53 ± 1.45	2.07 ± 1.24	.445	2.06 ± 1.95	2.13 ± 1.019	.917
Glucose fasting level (mg/dL)	118.75 ± 48.66	101.78 ± 25.23	.372	142.11 ± 81.37	85.33 ± 9.29	.002
Ammonia (μg/d)	–	–	–	95.15 ± 52.2	69.8 ± 17	.011
ACE-III total score (%)	83.25 ± 5.65	94.43 ± 2.68	.001	68.61 ± 12.9	92.33 ± 0.58	.000
Attention (%)	93.6 ± 6.3	96.09 ± 6.82	.368	82.25 ± 13.7	100.00 ± 0.00	.000
Memory (%)	77.13 ± 7.72	94.04 ± 6.1	.000	57.14 ± 22.62	84.33 ± 6.35	.001
Verbal fluency (%)	73.25 ± 13.81	87.48 ± 7.69	.023	62.21 ± 19.80	90.67 ± 8.08	.004
Language (%)	89.38 ± 10	97.57 ± 3.76	.055	82.07 ± 13.80	96.00 ± 4.00	.003
Visuospatial abilities (%)	80.5 ± 19.96	94.13 ± 8.68	.099	55.43 ± 18.95	91.67 ± 9.71	.006

The *p* values based on *t*-test of equality of means.
Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CI, cognitive impairment; eGFR, creatinine levels and creatinine clearance; GGTP, gamma-glutamyl transferase; non-CI, noncognitive impairment; TSH, thyroid-stimulating hormone.

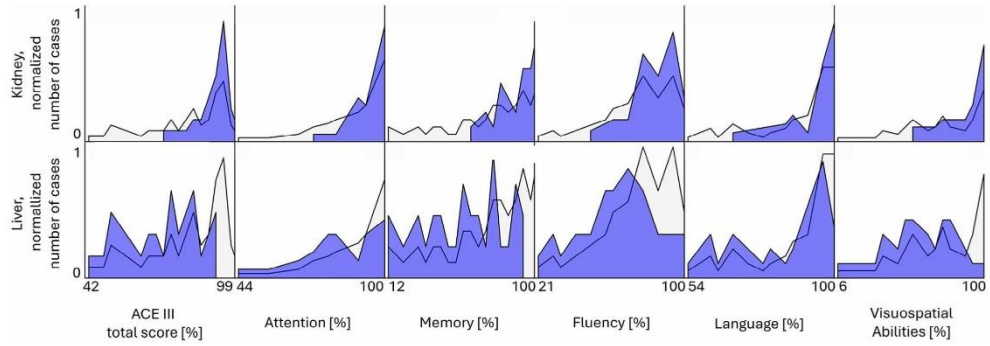

FIGURE 1 Distributions of normalized scores of Addenbrooke's Cognitive Examination-III (ACE-III) test and its individual cognitive domains attention, memory, fluency, language, and visuospatial abilities (columns) in patients with end-stage kidney disease (ESKD; kidney)—upper row, and alcohol-related liver cirrhosis (liver)—lower row. Light gray area—distributions for all participants (kidney and liver patients together), dark area—distributions for a given group (kidney or liver). The scale of gray is different in upper and lower row due to normalization.

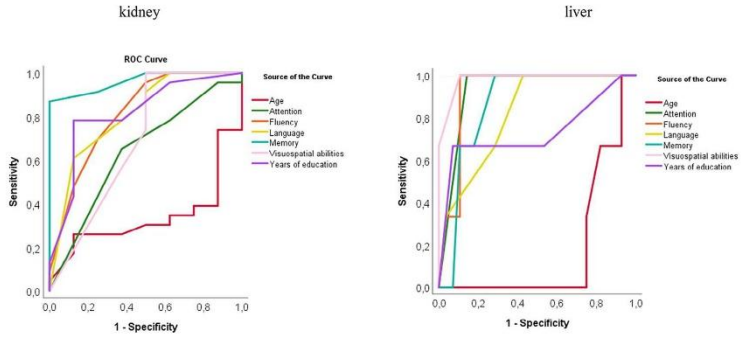

FIGURE 2 Receiver operating characteristics (ROC) curves for classifying patients without cognitive impairment based on various parameters (age, years of education, total results of the Addenbrooke's Cognitive Examination-III [ACE-III] test as well as the results of each domain of the ACE-III test).

TABLE 2 Values of area under the receiver operating characteristics (ROC) curve (AUC) for classification patients without cognitive impairment based on age, years of education, total results of the Addenbrooke's Cognitive Examination-III (ACE-III) test, and the results of each domain of the ACE-III test.

Test result variable(s)	Kidney AUC	Liver AUC
Age, years	0.237	0.179
ACE-III test	1.000	1.000
Attention	0.625	0.929
Memory	0.962	0.863
Verbal fluency	0.813	0.923
Language	0.810	0.821
Visuospatial abilities	0.700	0.928
Years of education	0.813	0.738

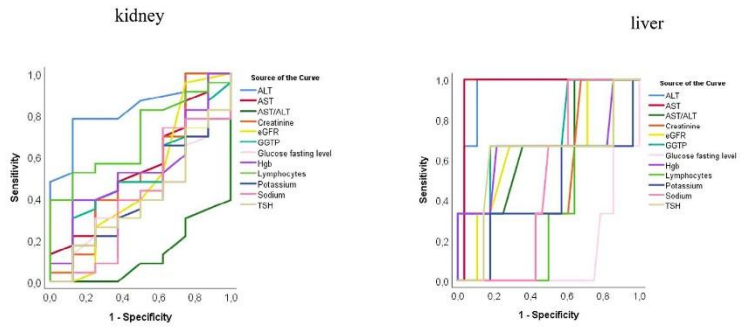

FIGURE 3 Receiver operating characteristics (ROC) curves for classifying patients without cognitive impairment based on various blood test parameters. Max values of area under the curve (AUC) for ALT (AUC = 0.834) and TLC (AUC = 0.698) in end-stage kidney disease (ESKD) group, while in alcohol-related liver cirrhosis group, the best indicators for classification were AST (AUC = 0.964) and ALT (U/L; AUC = 0.940). ALT, alanine transaminase; AST, aspartate aminotransferase; eGFR, creatinine clearance; GGTP, gamma-glutamyl transferase; TSH, thyroid-stimulating hormone.

TABLE 3 Area under the receiver operating characteristics (ROC) curve (AUC) values for classifying patients without cognitive impairment based on various blood test parameters.

Test result variable(s)	Kidney AUC	Liver AUC
Hemoglobin (g/dL)	0.541	0.655
AST (U/L)	0.554	0.964
ALT (U/L)	0.834	0.94
AST/ALT ratio	0.125	0.685
GGTP (U/L)	0.497	0.696
Creatinine (mg/dL)	0.533	0.429
eGFR (mL/min/1.73 m^2)	0.478	0.649
Sodium (mmol/L)	0.408	0.494
Potassium (mmol/L)	0.405	0.429
TSH (uIU/mL)	0.397	0.613
Glucose fasting level (mg/dL)	0.394	0.125
TLC (10^3/μL)	0.698	0.333

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; eGFR, creatinine clearance; GGTP, gamma-glutamyl transferase; TLC, total lymphocyte count; TSH, thyroid-stimulating hormone.

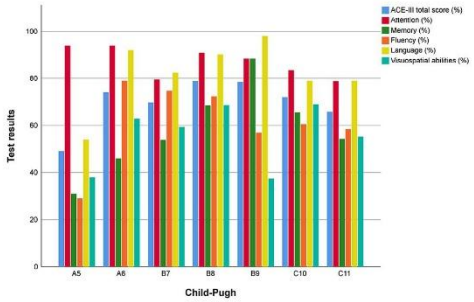

FIGURE 4 Addenbrooke's Cognitive Examination-III (ACE-III) test results and in single cognitive domains depending on the Child–Pugh score. A clearer trend is evident only in the attention domain (red bars), in which the test values decrease slightly as the Child–Pugh score increases. Class A, 5–6 points: well compensated cirrhosis; Class B, 7–9 points: mild decompensated cirrhosis; Class C, 10–15 points: severe decompensated cirrhosis.

The other parameters, that is, creatinine levels, creatinine clearance, Hgb levels, TSH, glucose fasting levels, sodium and potassium levels, GGTP, as well as AST in the ESKD group and TLC in the group with alcoholic cirrhosis (the corresponding ROC curves were much closer to the reference line)—had AUC values closer to 0.5, that is, poor predictive accuracy (Table 3). Furthermore, a tendency toward poorer test results in the memory domain was observed with increasing ammonia levels and liver disease severity (higher Child–Pugh scores, Figures 4 and 5). Also, Figure 6 shows the correlation between liver disease severity and cognitive performance. As the MELD-Na increased, cognitive performance on the ACE-III test decreased, though this was not statistically significant.

8 | DISCUSSION

8.1 | Summary of main results and comparison between other studies

Our study has demonstrated that among the patients awaiting transplantation, the prevalence of CI in patients with alcohol-related liver cirrhosis was much higher compared to patients with ESKD (90% vs. 26%). In patients with alcohol-related liver cirrhosis, all cognitive domains were significantly affected, with memory and visuospatial abilities being most impaired. On the other hand, in patients with ESKD, the most impaired domains were memory and verbal fluency, which reflects executive function impairment.

The results of the current study are consistent with the results of previous studies on the association between liver cirrhosis of mixed etiology and cognitive functioning. In a study of 80 patients with compensated liver cirrhosis of alcoholic etiology (n = 43) and compensated liver cirrhosis of viral etiology (n = 37), more patients with alcoholic compensated liver cirrhosis had impairments in memory and the domain of visuospatial abilities compared with the patients with viral compensated liver cirrhosis (Lee et al., 2016). A previous study of 280 patients with mixed causes of end-stage liver disease, including 46 patients with alcoholic liver disease, found the most striking impairments to be noted in the domains of attention, immediate memory, and visuospatial construction. Moreover, the prevalence of neuropsychological impairment was highest among patients with liver disease secondary to alcohol abuse (Sorrell et al., 2006).

On the other hand, as we have shown in previously published studies, CI is common in ESKD patients undergoing renal replacement therapy, with prevalence ranging from 30% in kidney transplant recipients, 33% in patients undergoing peritoneal dialysis, to 58% in patients undergoing hemodialysis (Golenia et al., 2023a, 2023b, 2023c), with verbal fluency and memory being the most impaired domains. It should

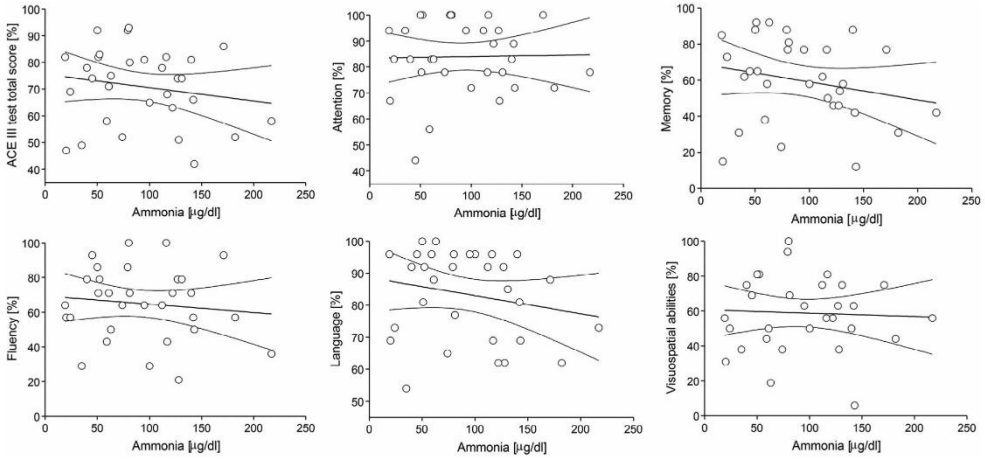

FIGURE 5 Dependence of total Addenbrooke's Cognitive Examination-III (ACE-III) test results and in single cognitive domains attention, memory, fluency, language, and visuospatial abilities on ammonia level in a group of alcohol-related liver cirrhosis (liver). Linear regression lines (and 95% confidence intervals) indicate a decreasing trend although it is not statistically significant.

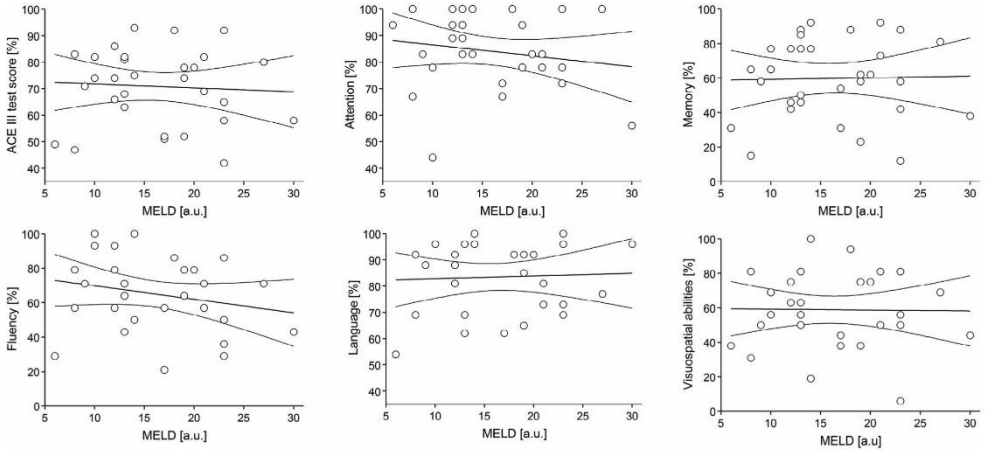

FIGURE 6 Dependence of the Addenbrooke's Cognitive Examination-III (ACE-III) test results and its single domains attention, memory, fluency, language, and visuospatial abilities on the Model for End-Stage Liver Disease (MELD) scale result in a group of alcohol-related liver cirrhosis (liver). Linear regression lines (and 95% confidence intervals) indicate a decreasing trend although it is not statistically significant.

also be noted that CI was found in 55% of a total of 349 dialysis patients evaluated for kidney transplantation, prior to being placed on the active list, and CI was associated with a lower likelihood of being listed for kidney transplantation as well as a longer waiting time for transplantation (Gupta et al., 2019). The median time to active listing for patients with CI was longer compared to patients without CI (10.6 months vs. 6.3 months; Gupta et al., 2019). Similarly, the results of another study showed that patients with ESKD who were cognitively impaired were less likely to be listed, and the median time between dialysis initiation and listing was greater among these patients than in those who did not have CI (11.7 months vs. 4.0 months; Chu et al., 2020).

In our study, the most significant increase in the prevalence of CI was found in patients with lower educational attainment, in both

ESKD and alcohol cirrhosis groups, and in elderly patients, but only in the alcohol cirrhosis group. Cognitive abilities are widely recognized to be impacted positively by education levels and negatively by age (Schneeweis et al., 2014). Higher levels of education typically improve cognitive outcomes in several ways, for example, through lifestyle choices, health behaviors, social interactions, labor force participation, type of occupation, and brain development (Schneeweis et al., 2014). Conversely, cognitive functioning declines with normal aging, particularly for cognitive tasks that require the rapid processing or transformation of information to make decisions, for example, processing speed, working memory, and executive cognitive functions (Murman, 2015).

Furthermore, we showed that lower ALT and TLC levels in ESKD patients and lower AST and ALT levels in patients with alcohol cirrhosis negatively affected the ACE-III test results. If we consider TLC to be a nutritional marker (Leandro-Merhi et al., 2017), malnutrition may lead to poorer results on cognitive tests. It has also been reported that lower ALT and AST levels are associated with hepatic hypometabolism and result in reduced brain glucose metabolism, impaired neurotransmitter production and synaptic maintenance, systemic insulin resistance and inflammation, and may lead to increased prevalence of dementia (Lu et al., 2021).

We also observed a trend toward poorer performance on cognitive tests in the memory domain as serum ammonia levels and the severity of liver disease increased, as measured by the Child–Pugh score. It is well known that an increase in ammonia levels in the brain can lead to synaptic dysfunction and neurotransmitter imbalance, resulting in memory loss (Jo et al., 2021). Finally, the ACE-III test results were correlated with disease severity as measured by MELD-Na score, that is, more advanced disease was associated with poorer cognitive performance.

8.2 | Possible mechanism contributing to CI in ESKD and alcoholic liver disease

Although the precise mechanisms linking alcoholic cirrhosis and ESKD to CI are not yet well understood, the association may be partly explained. First, alcohol cirrhosis induces neuroinflammation in the brain, notably in the hippocampus, which may contribute to cognitive decline (King et al., 2020). Second, it is well known that brain magnetic resonance imaging (MRI) shows reduced hippocampal volume in patients with alcohol use disorders compared to healthy controls (Zahr & Pfefferbaum, 2017). The hippocampus is involved in memory and learning processes, as well as emotional regulation, by interaction with other brain structures such as the prefrontal cortex, the amygdala, and the nucleus accumbens (Wilson et al., 2017). Third, chronic alcohol abuse may cause damage to the frontal cortex, for example, by increasing the levels of inflammatory cytokines such as tumor necrosis factor alpha (TNFα), interleukin 6 (IL6), monocyte chemoattractant protein 1 (MCP1), and interleukin 1 beta (IL1β) in the prefrontal cortex areas of the brain (King et al., 2020; Zahr & Pfefferbaum, 2017), all responsible for maintaining spatial working memory (van Asselen et al., 2006).

Furthermore, cerebral and glomerular small vessel disease is considered to be one of the causes of cognitive decline in chronic kidney disease (CKD; Mogi & Horiuchi, 2011). Patients with CKD have an increased burden of white matter hyperintensity, silent brain infarction, lacunar infarction, and cerebral microbleeds, which are markers of cerebral small vessel disease and can be detected by brain MRI (Mogi & Horiuchi, 2011). Additionally, there is a well-documented strong association between cerebral small vessel disease and diminished cognitive functioning in CKD patients (Wei et al., 2022).

Another plausible mechanism that could contribute to CI in CKD patients is the nonvascular hypothesis involving purine nucleotides, oxidative stress, and fibroblast growth factor 23 (FGF23)-related pathways, as well as the accumulation of uremic toxins, such as phosphate, indoxyl sulfate (IS), and para-cresyl sulfate (PCS), which are agonists of the transcription factor, that is, the aryl hydrocarbon receptor (AhR), in endothelial cells (Xie et al., 2022). All this may lead to the disruption of the blood–brain barrier and, consequently, increased transport of uremic toxins, inflammatory and procoagulant mediators to the brain, which may lead to the deterioration of cognitive functions (Xie et al., 2022).

Also, oxidative stress, one of the important factors in aging-related Alzheimer's disease, leads to the cleavage of the amyloid precursor protein (APP) and amyloid beta (Aβ) production/accumulation, accelerating the occurrence of CI (Xie et al., 2022). Additionally, elevated FGF23 levels directly affect hippocampal neurons or disrupt the immune system, impairing memory and learning functions (Xie et al., 2022).

Finally, dysbiosis, which refers to changes in the composition of the gut microbiota, may be another explanation for CI in both ESKD and alcoholic liver disease (Feng et al., 2021). Still, little is known about whether dysbiosis precedes the diseases and serves as an etiological factor, or whether it is merely a comorbid state (Fairfield & Schnabl, 2020; Feng et al., 2021). Among patients with CKD, dysbiosis can affect the course of the disease by increasing proinflammatory cytokines as well as leading to the accumulation of uremic toxins. Both of these factors consequently cause chronic neuroinflammation (Feng et al., 2021; Lee et al., 2023). Moreover, in the course of alcoholic liver disease, the composition of the gut microbiota is constantly changing in parallel with the progression of the disease (Fairfield & Schnabl, 2020). Dysbiosis may be a factor associated with chronic inflammation, although it may serve to deregulate bile acid metabolism, leading to toxin accumulation and subsequent liver failure (Fairfield & Schnabl, 2020). Even though a few studies have highlighted the interrelationship between dysbiosis and CI (Pei et al., 2023), there have been no extensive studies analyzing changes in gut microbiota as a factor affecting cognitive function in both ESKD and alcoholic liver disease.

8.3 | Limitation

There are several limitations to this study. First, its cross-sectional design, making it impossible for the results to be used to demonstrate causality. Second, the study groups were relatively small, and

the results of our study may be false positives, so they should be treated with caution. Third, a healthy control group was not included in the study. However, to our knowledge, this is the first study in Poland on cognitive function assessment in patients with ESKD and alcohol-related liver cirrhosis listed for solid organ transplantation. Additionally, the ACE-III test has a high sensitivity and specificity for detecting CI (Kaczmarek et al., 2022) and is easy to use in outpatient clinics as well as in dialysis units.

The strength of this study lies in the fact that patients with alcoholic cirrhosis included in the study constituted a homogeneous group with the same alcohol-related etiology of liver disease, which significantly increases the credibility of our results by excluding disease-related confounding factors that may influence cognitive test results. Homogeneous populations are more often representative than heterogeneous ones, and the more valid conclusions can be drawn even from a small sample (Jager et al., 2017).

9 | CONCLUSION

The prevalence of CI, especially in patients with alcohol-related liver cirrhosis, is high and can be a significant clinical problem, negatively affecting the transplantation process. Routine screening tests in this group would contribute to the implementation of appropriate management, such as rehabilitation program or psychosocial treatments and facilitate the provision of specialized health care.

AUTHOR CONTRIBUTIONS

Aleksandra Golenia: Conceptualization; writing—original draft; methodology; writing—review and editing. **Piotr Olejnik**: Investigation; data curation. **Magdalena Grusiecka-Stańczyk**: Investigation. **Norbert Żołek**: Formal analysis; writing—review and editing. **Ewa Wojtaszek**: Investigation. **Paweł Żebrowski**: Investigation. **Joanna Raszeja-Wyszomirska**: Supervision; writing—review and editing. **Jolanta Małyszko**: Supervision; conceptualization; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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PEER REVIEW

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Cognitive Performance in Patients With Alcohol-Associated Liver Disease Undergoing Liver Transplantation

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Cognitive impairment (CI) in alcohol-related liver cirrhosis (ALD) is often underestimated, primarily attributed to hepatic encephalopathy (HE), despite evidence suggesting that deficits may persist after liver transplantation (LT). This study assessed CI both before and after LT through a structured psychiatric evaluation. A total of 101 ALD patients listed for LT were assessed; 61 underwent transplantation. Three patients died pre-LT, and six post-LT, leaving 55 for longitudinal cognitive evaluation. The Addenbrooke's Cognitive Examination III (ACE III) was administered at LT listing and 7.1 months post-LT. Pre-LT CI was prevalent, with 86% scoring below the ACE III threshold. Mild cognitive impairment (MCI) was observed in 33%, and 52% had a high probability of dementia. Post-LT, ACE III scores improved (Δ +7.07 ± 8.47, $P < 0.01$), with the greatest gains in memory (+1.46, $P = 0.01$) and verbal fluency (+1.43, $P = 0.02$), while attention remained largely unchanged. Despite overall cognitive recovery, persistent deficits were observed, particularly in executive function and fluency. LT improves cognition, but persistent deficits suggest CI in ALD is not entirely reversible. These findings underscore the need for targeted cognitive interventions before and after LT.

Keywords: alcohol-related liver disease, cognitive impairment, liver transplantation, blood ammonia level, hepatic encephalopathy

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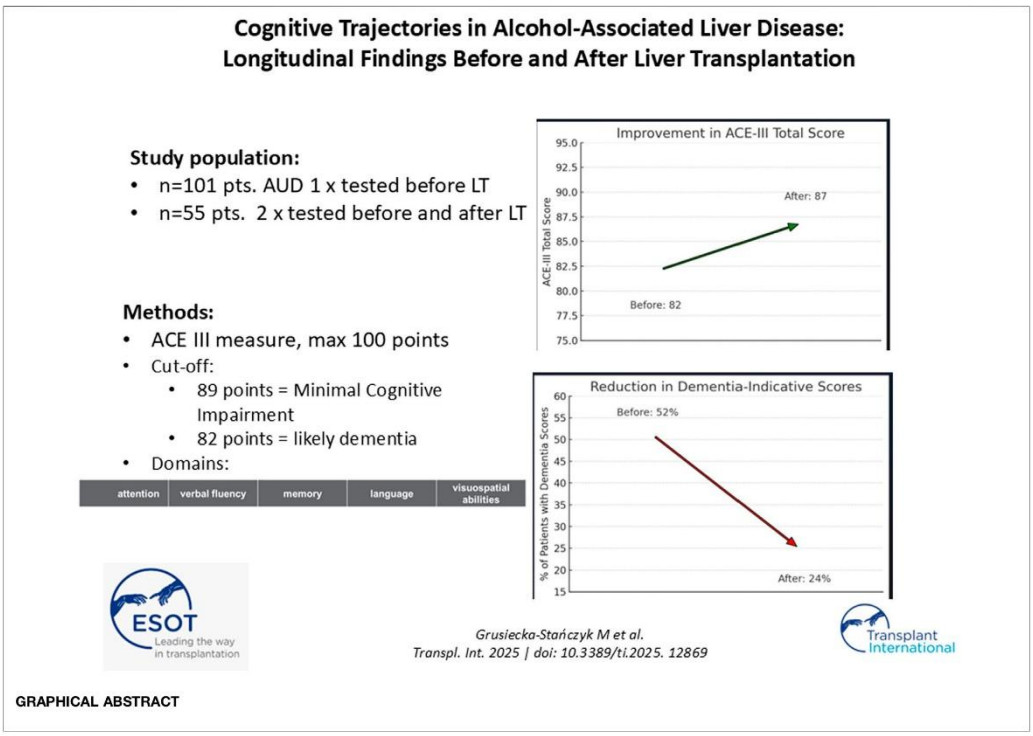
INTRODUCTION

Alcohol is the most widely abused psychoactive substance globally, with high-risk drinking reported in up to 30% of Western populations, contributing substantially to morbidity and mortality [1]. Alcohol use disorder (AUD), as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V), encompasses a spectrum of maladaptive drinking behaviors that result in clinically significant physical, psychological, or social dysfunction [2]. Excessive alcohol intake is a well-established cause of liver cirrhosis, which remains a leading indication for liver transplantation (LT), particularly in cases of severe alcoholic hepatitis and end-stage liver disease (ESLD) [3, 4].

Cirrhosis-related neurocognitive decline is commonly attributed to hepatic encephalopathy (HE), a complication of advanced liver dysfunction associated with hyperammonemia and disruption of the liver-brain axis [5, 6]. While blood ammonia levels are a recognized biomarker of HE, they



GRAPHICAL ABSTRACT

primarily have a high negative predictive value and do not reliably correlate with cognitive impairment (CI) [5, 6]. Although HE is considered reversible after LT, studies indicate that some patients with overt HE pre-transplantation exhibit persistent or even worsening cognitive deficits post-LT, suggesting that CI may result from more complex and multifactorial mechanisms [7, 8].

In patients with AUD, cognitive deficits extend beyond HE. Chronic alcohol consumption leads to widespread and potentially irreversible neurotoxic effects, including oxidative stress, mitochondrial dysfunction, and neuroinflammation. Acetaldehyde, the primary metabolite of ethanol, induces cellular damage by forming protein adducts and generating reactive oxygen species, which impair mitochondrial DNA and neuronal integrity [9]. Concurrently, elevated levels of pro-inflammatory cytokines—such as TNF-α, IL-6, IL-1β, and MCP1—are known to disrupt neuroplasticity and contribute to structural and functional changes in key brain regions, including the hippocampus and prefrontal cortex [10, 11].

As a result, individuals with AUD are particularly susceptible to a broad spectrum of cognitive deficits, including impairments in executive function, attention, abstract reasoning, psychomotor speed, visuospatial skills, language, and both verbal and visual memory [12–14]. These deficits are often linked to alcohol-induced reductions in hippocampal white matter volume and damage to the prefrontal cortex—areas crucial for memory, decision-making, and behavioral regulation. Structural brain abnormalities, minimal and overt HE, chronic alcohol use, diabetes, and gut microbiome dysbiosis may further contribute to pre-transplant CI and could influence its persistence after LT [15, 16].

Despite these known associations, cognitive impairment in patients with alcohol-related liver cirrhosis awaiting LT remains under-investigated. Existing studies on CI in LT recipients with cirrhosis of mixed etiologies report a post-transplant prevalence of CI ranging from 0% to 36% [17], but they are limited by methodological inconsistencies, variable definitions of HE and CI, and heterogeneous patient populations. Additionally, most prior research originates from neurology or psychiatry domains, often employing diverse and non-standardized diagnostic tools, which complicates comparisons and limits clinical applicability [18–20].

To address these limitations, the present pilot study aimed to perform a structured, longitudinal evaluation of cognitive function in a homogeneous cohort of patients with AUD-related ESLD. By assessing cognition both at the time of listing and after liver transplantation in a single-center setting,

this study seeks to provide new insight into the nature, evolution, and clinical relevance of cognitive impairment in this vulnerable patient population.

Given the limited availability of long-term, prospective data on the trajectory of cognitive impairment (CI) in patients before and after liver transplantation (LT) - particularly in clinically homogeneous populations - two primary research objectives were formulated:

1. To conduct a quantitative and qualitative assessment of cognitive impairment prior to liver transplantation in patients with alcohol-related liver disease (ALD) qualified for transplantation within a single transplant center.
2. To analyze changes in cognitive function following liver transplantation, with particular emphasis on the dynamics and potential improvement of cognitive performance in this specific patient population.

PATIENTS AND METHODS

Between November 2022 and January 2024, a total of 101 consecutive adult patients with alcohol use disorder (AUD) were enrolled in the study (78% male; mean age: 53 ± 11 years; mean MELD score: 16 ± 7), all of whom were evaluated as potential candidates for liver transplantation (LT). Among them, 17% had hepatocellular carcinoma (HCC), while the remaining 83% were assessed for LT due to chronic liver failure.

Exclusion criteria included regular use of sedative medications, severe overt hepatic encephalopathy, and psychiatric or neurodegenerative disorders precluding cognitive assessment. No patients with acute alcoholic hepatitis were included in the study.

Plasma ammonia concentration was measured using an enzymatic method with glutamate dehydrogenase (GLDH) on the Dimension EXL analyzer (Siemens Healthineers, Forchheim, Germany), with a reference range of 19–55 μg/dL.

Of the 101 patients who underwent baseline cognitive assessment, 61 successfully received liver transplants. Three patients died before LT and an additional six died postoperatively. Ultimately, 55 individuals (including 14 women, 25%) underwent repeated cognitive evaluation (**Figure 1**). The mean age in this subgroup was 56 years.

All patients were routinely assessed during hospitalization by a psychiatrist dedicated to the transplant program, as part of the standard pre-transplant evaluation protocol. This included a comprehensive psychiatric consultation and administration of the Addenbrooke's Cognitive Examination III (ACE-III). In patients who completed both assessments, psychiatric evaluation was conducted at listing for liver transplantation and again at an average of 7.1 months post-transplantation (SD = 1.45; range: 6–11 months; median: 7 months), ensuring methodological consistency and enabling reliable longitudinal analysis.

Cognitive Functions Assessment

The Addenbrooke Cognitive Test III (ACE III) with a cut-off of 89 points for Mild Cognitive Impairment (MCI), and <82 points for a high probability of dementia was used to evaluate cognitive functions. The ACE III test covers five main domains of cognition, i.e., attention, verbal fluency, memory, language and visuospatial abilities, and is widely used, due to its specificity and sensitivity as well as simplicity and feasibility for administration, not only for physicians. The Polish version is available free of charge [21]. The ACE III was previously validated using standard neuropsychological tests [22]. Beside this, the center already has own experience in using this diagnostic tool, in the form of projects already published [23, 24].

Statistical Analyses

Statistical analyses were performed using SPSS (SPSS Statistics, version 28.0. IBM Corp., USA). Continuous variables are shown as mean ± standard deviation (SD) and categorical variables are expressed as absolute and relative (in per cent) frequencies. The Kolmogorov-Smirnov test was applied to determine whether continuous variables were normally distributed. The Wilcoxon Mann-Whitney U test or Student´s t-test were used for analyzing continuous variables. Chi^2 test and Fisher´s exact test were used for group comparisons of categorical variables. The correlations between ACE III results and clinical variables were evaluated by Spearman's rank correlation coefficient. The associations between ACE III result suggesting probability of dementia (ACE III <82 points) and clinical data were assessed by univariate and multivariate logistic regression analyses. Statistical procedures were performed two-sided and p-values <0.05 reflected to be statistically significant.

Ethics

Appropriate informed consent was obtained from each patient included in the study. The study protocol was approved by the Bioethics Committee of the Medical University of Warsaw (approval number KB/81/2022) and conforms with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

RESULTS

Preliminary Assessment of Cognitive Function

At the initial stage of the study, cognitive function was assessed in 101 individuals. Overall, cognitive impairment, as evaluated using the Addenbrooke's Cognitive Examination III (ACE-III), was observed in 86% of participants: 33% met the criteria for mild cognitive impairment (MCI), while 52% met the criteria indicating a high likelihood of dementia.

The mean total ACE-III score was 78.32 ± 11.99, ranging from 50 to 96, with a median of 79.0 (interquartile range [IQR]: 70.0–87.0).

Among the five cognitive domains assessed, the greatest deficits were observed in verbal fluency, followed by visuospatial abilities. The mean scores for attention, memory, language, and visuospatial skills were 16.11, 17.34, 22.43, and 11.84 points, respectively, with median scores of 17.0, 18.0, 23.0, and 12.0. Details are presented in **Table 1**. As variables followed

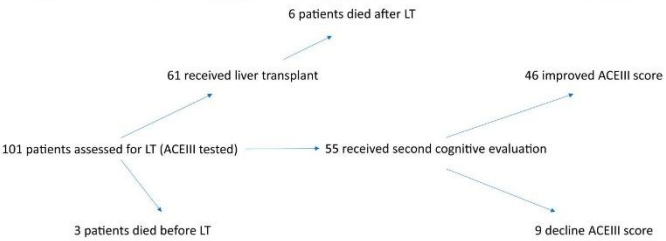


FIGURE 1 | Flow chart of patient inclusion, liver transplantation outcomes, and cognitive assessment results before and after transplantation.

TABLE 1 | ACE-III cognitive performance among liver transplant candidates with ALD.

N = 101	Age	Child-Pugh class	MELD	ACEIII	Attention	Memory	Fluency	Langugage	Visuo-spatial abilities	Years of education
Mean ±	52.54 ±	8.28 ± 1.94	16.0 ±	78.32 ±	16.11 ±	17.34 ±	10.21 ±	22.43 ± 3.98	11.84 ± 3.29	12.35 ± 2.91
SD	10.52		6.56	11.99	1.96	4.66	2.48			
median	53.0	8.0	14.0	81.0	17.0	18.0	10.0	24.0	12.0	12.0
range	24–73	5–14	6–41	42–100	8–18	3–26	3–14	4–26	1–17	8–20
IQR	45–61	7–10	11–20	71–86	15–18	15–20	9–12	21–25	10–15	10–13

non-normal distributions (as per Kolmogorov–Smirnov test), both means (±SD) and medians (IQR) are reported for all ACE III subdomains to enhance interpretability.

The mean venous blood ammonia concentration was 86 ± 57 μg/dL, with hyperammonemia (>55 μg/dL) observed in 45% of patients. As shown in **Table 1**, patients exhibiting signs of dementia had significantly shorter education duration ($P < 0.001$) and higher Child-Pugh scores ($P = 0.04$). However, no other clinical differences were identified—such as ammonia level or MELD score—when compared to patients with ACE-III scores >82.

The likelihood of dementia was significantly higher in patients with alcohol-related liver disease (ALD) alone compared to those with ALD and concomitant hepatocellular carcinoma (HCC) ($P = 0.015$). Among the 17 patients with ALD + HCC, 4 (23.5%) had ACE-III scores below 82, indicating a high probability of dementia. In contrast, 52% of patients in the ALD-only group fell below this threshold.

A total of ten deaths were recorded in the cohort, with a trend toward higher mortality among patients scoring <82 on the ACE-III (15%) versus those scoring ≥82 (4%), though this did not reach statistical significance ($P = 0.066$), as shown in **Table 2**. Moreover, 76 individuals (75%) were listed for liver transplantation, but no significant differences were observed in ACE-III total scores or individual cognitive domains based on transplant listing status.

The mean total ACE-III score in the entire cohort was 78 ± 12 points, with the lowest scores observed in the domains of verbal fluency and visuospatial abilities. The ACE-III score was significantly correlated with years of education and the Child-Pugh score, as shown in **Table 3**.

Notably, the overall MELD score was not associated with the total ACE-III score; however, it showed a significant correlation with the attention and language subdomains of the ACE-III (**Table 3**). Additionally, age was negatively correlated with the verbal fluency subscale and showed a negative trend in relation to the overall ACE-III score (**Table 3**).

Multivariable analysis demonstrated that both the Child-Pugh score (OR 1.51; 95% CI: 1.14–2.00) and years of education (OR 0.65; 95% CI: 0.53–0.79) were independently associated with ACE-III scores below 82 points, indicating a high likelihood of dementia (**Table 4**). In contrast, age, sex, blood ammonia level, presence of hyperammonemia, and MELD score showed no significant association with ACE-III scores <82.

Results of Repeated Cognitive Assessment (N = 55 Patients)

Cognitive Function Before Liver Transplantation

Before transplantation, the mean ACE-III score was 80.62 ± 10.40, with a median of 82.0 (range: 51–97; IQR: 75.0–87.0). Among the assessed cognitive domains, the language domain was best preserved (mean: 23.19 ± 3.44), while the greatest deficits were observed in verbal fluency (mean: 10.21 ± 2.48). Memory and visuospatial abilities showed moderate performance (memory: 18.15 ± 4.16; visuospatial: 12.22 ± 3.15). The mean attention score was 16.38 ± 1.39.

The average number of years of education in this group was 12.19 ± 3.24.

Data are presented in **Table 5**.

Cognitive Function After Liver Transplantation (n = 55 Patients)

An overall improvement in cognitive function was observed following liver transplantation. The mean ACE-III score

TABLE 2 | Clinical characteristics of the study group and subgroups with positive and negative screening results for suspected dementia based on the ACE-III test (i.e., <82 points).

	Entire cohort	ACE III positive for dementia suspicion	ACE III negative for dementia suspicion	P – value
N, %	101 (100%)	53 (52.5%)	48 (47.5%)	-
Age, years	52.5 ± 10.5	53.3 ± 10.0	51.7 ± 11.1	0.304
Females, n (%)	22 (21.8%)	11 (20.8%)	11 (22.9%)	0.814
MELD (points)	16.0 ± 6.6	16.9 ± 7.0	15.0 ± 6.0	0.114
Child-Pugh (points)	8.3 ± 1.9	8.7 ± 1.9	7.9 ± 2.0	0.044
Blood ammonia, ng/mL	85.5 ± 56.8	82.8 ± 45.8	88.6 ± 67.5	0.961
Years of education	12.4 ± 2.9	11.2 ± 2.2	13.7 ± 3.1	<0.001
ACE III, points	78.3 ± 12.0	70.1 ± 10.8	87.4 ± 4.2	<0.001
Death, n (%)	10 (10%)	8 (15%)	2 (4%)	0.066

Abbreviations: ACE-III, Addenbrooke's Cognitive Examination III; MELD, Model for End-Stage Liver Disease score.

TABLE 3 | Correlations between variables and ACE-III total and domain scores, presented as rho values.

	Total ACE III	Attention ACEIII	Verbal fluency ACEIII	Memory ACEIII	Language ACE III	Visuospatial abilities ACEIII
Age	−0.190	−0.098	−0.262**	−0.136	−0.146	−0.129
Female	0.016	−0.022	0.008	−0.044	−0.030	0.118
Education period	0.390**	0.225*	0.077	0.417**	0.139	0.266**
Child-Pugh score	−0.262**	−0.320**	−0.253*	−0.121	−0.270**	−0.200*
MELD score	−0.161	−0.240*	−0.177	−0.098	−0.251*	−0.076
Blood ammonia level	−0.075	−0.063	−0.091	−0.063	−0.056	−0.132
Total ACE III	1	0.522**	0.714**	0.717**	0.601**	0.746**

Abbreviations: ACE-III, Addenbrooke's Cognitive Examination III; MELD, Model for End-Stage Liver Disease score. Rho values were calculated using Spearman's rank correlation coefficient, and p values <0.05 were considered statistically significant.
** –p < 0.05; ** –p < 0.001.*

TABLE 4 | Logistic regression analysis for ACE-III scores <82 in patients with alcohol-related liver cirrhosis.

	Univariable		Multivariable	
	P value	OR (95% CI)	*P* value	OR (95% CI)
Years of education	<0.001	0.70 (0.59–0.84)	<0.001	0.65 (0.53–0.79)
Child-Pugh score	0.039	1.25 (1.01–1.55)	0.004	1.51 (1.14–2.00)
MELD score	0.133	1.05 (0.99–1.12)	-	
Age	0.413	1.02 (0.98–1.05)	-	
Blood ammonia	0.612	1.00 (0.99–1.01)	-	
Hiperammonemia	0.732	0.87 (0.40–1.92)	-	
Females	0.793	0.88 (0.34–2.27)	-	

Abbreviations: ACE-III, Addenbrooke's Cognitive Examination III; MELD, Model for End-Stage Liver Disease score; OR, odds ratio.

increased to 87.0 ± 6.7 points, with a median of 86.0 (range: 73–98; interquartile range [IQR]: 83.0–91.0).

The most notable improvements were seen in memory (mean: 20.83 ± 3.88; median: 21.0) and verbal fluency (mean: 12.08 ± 1.56; median: 12.0). Improvement was also evident in attention (mean: 17.0 ± 1.18), language (mean: 23.85 ± 2.23), and visuospatial abilities (mean: 13.93 ± 2.14). Data are presented in **Table 6**.

Changes in Cognitive Function Following Liver Transplantation (Δ Scores)

Following liver transplantation, patients exhibited a mean increase of 7.07 ± 8.47 points in total ACE-III scores (median: +5.0; range: −10 to 34; interquartile range [IQR]: 2.0–9.0). The most pronounced improvements were observed in the following cognitive domains:

- Memory: +1.46 ± 2.91 (median: +1.0; range: −7 to 10; IQR: 0.0–3.0)
- Verbal Fluency: +1.43 ± 1.89 (median: +2.0; range: −3 to 6; IQR: 0.0–2.0)
- Visuospatial Abilities: +1.52 ± 2.57 (median: +2.0; range: −5 to 7; IQR: 0.0–3.0)
- Attention: +0.71 ± 1.23 (median: +1.0; range: −3 to 4; IQR: 0.0–1.0)
- Language: +0.32 ± 2.54 (median: 0.0; range: −4 to 14; IQR: −1.0–1.0)

A Wilcoxon signed-rank test confirmed that the observed post-transplant improvement in total ACE-III scores was statistically significant ($Z \approx 420.0$, $p < 0.0001$), indicating that the changes were unlikely to have occurred by chance. Moreover, statistically significant gains were also observed across most individual subdomains (*all* $p < 0.01$), further supporting the robustness of the cognitive recovery pattern.

Among the 55 patients assessed, 42 (76%) demonstrated cognitive improvement, 9 (16%) experienced decline, and 4 (8%) remained stable. This distribution was also statistically significant (Wilcoxon signed-rank test, $p < 0.01$) and is depicted in **Figure 2**.

Test	Z/W-statistic	p-value
Wilcoxon	≈ **420.0**	**< 0.0001**

Cognitive Decline After Liver Transplantation

Although the overall trajectory pointed toward cognitive improvement, a decline in total ACE-III scores was observed in 16.4% of patients (9 out of 55). Specific cognitive domains most frequently affected by post-transplant deterioration included:

- Language–decline in 29.1% of patients (16/55)
- Memory–decline in 20.0% of patients (11/55)
- Attention–decline in 16.4% of patients (9/55)
- Verbal Fluency–decline in 14.5% of patients (8/55)
- Visuospatial Abilities–decline in 10.9% of patients (6/55)

The overall distribution of cognitive change categories is illustrated in **Figure 3**, showing that the majority of patients (n = 42; 76%) demonstrated post-transplant cognitive improvement, while 16% (n = 9) experienced decline and 7% (n = 4) remained unchanged (**Figure 3**).

Exploratory Comparison: Improved vs. Declined Cognitive Trajectory

To further explore factors associated with cognitive outcomes following liver transplantation, we performed an exploratory subgroup analysis comparing patients who demonstrated cognitive improvement with those who experienced decline, based on changes in total ACE-III scores 6 months post-transplant. On average, patients in the improved group were younger (55.4 ± 8.8 vs. 59.3 ± 7.4 years) and had more years of education (12.7 ± 2.9 vs. 11.4 ± 3.1 years). The difference in educational attainment between the groups reached statistical significance (Mann–Whitney U, $p = 0.045$), while the difference in age did not ($p = 0.165$).

In a broader comparison including patients with no change in cognitive performance (n = 4), Kruskal–Wallis testing revealed a trend toward significance for years of education ($p = 0.072$), with age differences remaining non-significant ($p = 0.148$). These findings suggest that educational background may play a role in cognitive recovery after liver transplantation, although results should be interpreted cautiously due to the limited sample size. A summary of this exploratory analysis is presented in **Table 7**.

DISCUSSION

This study provides a comprehensive evaluation of cognitive function at the time of liver transplant listing and in the early post-transplant period in a homogeneous cohort of patients with alcohol use disorder (AUD)-related liver cirrhosis. Cognitive impairment (CI) is increasingly recognized in patients with end-stage liver disease (ESLD), but available data remain heterogeneous, encompassing mixed etiologies, various diagnostic tools, and differing disease severity. Thus, a critical gap persists in understanding the true prevalence and profile of CI in well-defined liver transplant candidate populations.

To the best of our knowledge, this is the first study to examine cognitive performance both before and after liver transplantation (LT) in a cohort exclusively composed of patients with AUD-related ESLD. It delivers new insights into a crucial yet underexplored dimension of peri-transplant care. A recent review by Siddiqui et al. [17] included 24 studies with a median of 30 patients per study and follow-up ranging from 1 month to 1.8 years post-LT. The prevalence of CI varied from 4% to 36% within the first 8 months post-transplant and from 0% to 16% thereafter. Due to methodological variability, CI was grouped into six cognitive domains: attention, executive functions, working memory, long-term memory, language, and visuospatial abilities. However, no prior study has provided precise pre-LT CI data specifically in AUD candidates.

TABLE 5 | ACE-III results among liver transplant recipients with alcohol-related liver disease (ALD).

N = 55	Age	ACEIII 1	Attention 1	Memory 1	Fluency 1	Language 1	Visuo-spatial abilities 1	Year of education
Mean ±SD	53.19 ± 9.72	80.62 ± 10.40	16.38 ± 1.39	18.15 ± 4.16	10.21 ± 2.48	23.19 ± 3.44	12.22 ± 3.15	12.19 ± 3.24
median	53.0	82.0	17.0	19.0	10.0	24.0	13.0	12.0
range	32–74	51–97	12–18	8–25	3–14	10–26	3–16	8–20
IQR	46.0–60.0	75.0–87.0	16.0–18.0	16.0–22.0	9–12	21.0–25.0	10.0–14.0	10.0–14.0

TABLE 6 | Second ACE-III assessment in liver transplant recipients with alcohol-related liver disease (ALD).

N = 55	ACEIII 2	Attention 2	Memory 2	Fluency 2	Language 2	Visuo-spatial abilities 2	Time form LT (months)
Mean ±SD	87.0 ± 6.7	17.0 ± 1.18	20.83 ± 3.88	12.08 ± 1.56	23.85 ± 2.23	13.93 ± 2.14	7.13 ± 1.45
median	86.0	17.0	21.0	12.0	25.0	14.0	7.0
range	73–98	13–18	10–25	9–14	15–26	7–16	6–11
IQR	83.0–91.0	16.0–18.0	18.0–24.0	11.0–13.0	22.0–25.0	13.0–15.0	6.0–8.0

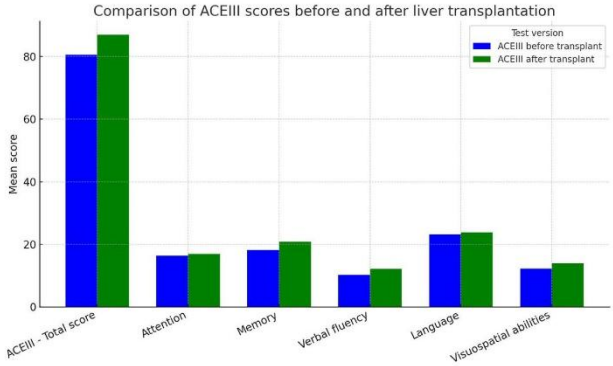


FIGURE 2 | ACE-III scores before and after liver transplantation in recipients with alcohol-related end-stage liver disease.

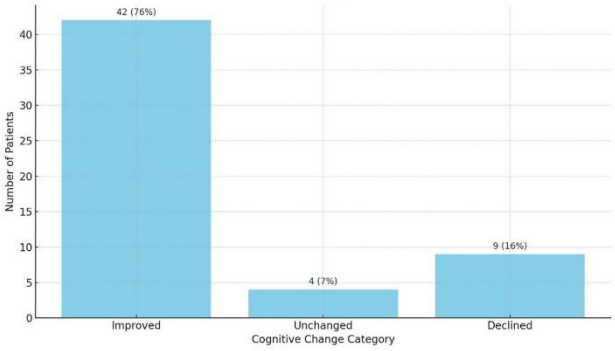


FIGURE 3 | Distribution of cognitive change categories after liver transplantation based on ACE-III scores (n = 55). Cognitive improvement was observed in 42 patients (76%), decline in 12 (22%), and no change in 1 patient (2%).

Our single-center analysis demonstrated a strikingly high prevalence of significant CI suggestive of dementia, with only 14% of patients scoring within the normal range on the ACE-III. The lowest performance was noted in verbal fluency and visuospatial domains, echoing findings by Lee et al. [25] and Sorrell et al. [26], who reported deficits in memory, visuospatial construction, attention, and immediate memory in patients with alcohol-related cirrhosis. Prior work by our group also showed significantly higher ACE-III scores and lower CI prevalence in patients with end-stage kidney disease (ESKD) compared to those with ESLD, with memory and visuospatial function being particularly impaired in the ESLD cohort [27].

Alcohol-induced brain damage is influenced by the quantity, age of onset, and duration of drinking, along with age, education, genetics, and prenatal exposure [14, 20, 28]. Stavro et al. [29] and Crowe et al. [28] described diffuse cognitive deficits in AUD, consistent with our cohort's mean ACE-III score of 78, with dysfunction across all domains. Verbal fluency and visuospatial impairments were particularly prominent, aligning with findings from Crowe et al. [28] and others [30–34]. Post-transplant studies by Campagna et al. [15] and Siddiqui et al. [17] also reported persistent deficits in attention, executive function, memory, and visuospatial processing.

Although the pathophysiological mechanisms linking ESLD and CI remain complex, factors such as neuroinflammation, hippocampal atrophy, and oxidative damage to the prefrontal cortex have been implicated [13, 35, 36]. MRI studies have shown reduced hippocampal volume in AUD patients compared to healthy controls [37]. Our data revealed a significant negative correlation between age and verbal fluency, with a trend toward

TABLE 7 | Comparison of patients with improved vs. declined cognitive performance post-transplant.

Group	N	Age (mean ± SD)	Education years (mean ± SD)
Improved	12	55.4 ± 8.8	12.7 ± 2.9
Declined	9	59.3 ± 7.4	11.4 ± 3.1
No change	4	52.0	10.5
p-value (Kruskal-Wallis)		0.148	0.072
p-value (Mann–Whitney U)		0.165	0.045

Due to non-normal distribution and small sample sizes, non-parametric tests were used: Kruskal–Wallis for three-group comparisons and Mann–Whitney U for pairwise testing.

lower total ACE-III scores in older patients. This supports findings by Campagna et al. [15], who suggested a critical vulnerability window at ages 50–60, possibly reflecting cumulative alcohol-related neurotoxicity.

Educational attainment emerged as a protective factor against CI, with ACE-III scores positively correlated with years of education, in line with Schneeweis et al. [38]. Conversely, a higher Child-Pugh score was associated with poorer cognitive outcomes and an increased likelihood of dementia-range ACE-III results. The MELD score did not correlate with total ACE-III performance but did show associations with attention and language subdomains. This divergence may relate to MELD's omission of nutritional parameters like serum albumin. Chronic malnutrition and sarcopenia, common in advanced liver disease, are known contributors to cognitive dysfunction [39–41].

Our findings align with reports showing greater post-LT CI prevalence in patients with pre-transplant MELD scores of 22–26 (21%–36%) compared to those with scores of 11–19 (8%–13%) [16, 17]. These trends highlight the multifactorial burden of CI in advanced liver disease.

In our cohort of 55 patients who completed both pre- and post-transplant cognitive evaluations, we observed a significant overall improvement in ACE-III scores, with the most notable gains in memory, verbal fluency, and visuospatial domains. Language function showed only modest improvement and remained one of the most frequently impaired areas. These findings align with prior reports suggesting that LT may reverse cognitive deficits, particularly those associated with hepatic encephalopathy and systemic inflammation [15, 17]. The Wilcoxon signed-rank test confirmed the statistical significance of this improvement ($p < 0.0001$), further supporting the role of LT in promoting cognitive recovery in the majority of patients (**Figure 2**).

However, as illustrated in **Figure 3**, recovery was not universal - approximately 16% of patients experienced cognitive decline, most often in language and memory domains, while 8% remained unchanged. This variation highlights the need for long-term neurocognitive surveillance and for identifying risk factors associated with suboptimal outcomes.

Preliminary findings (**Table 7**) suggest that younger age and higher educational attainment may offer some protection against cognitive decline following liver transplantation. Given the high prevalence and clinical consequences of cognitive impairment in patients with alcohol-related end-stage liver disease, routine cognitive assessment during pre-transplant evaluation appears warranted. Early detection of individuals at increased risk could enable personalized cognitive support strategies and potentially enhance long-term clinical outcomes. CI has been shown to negatively impact treatment adherence, decision-making capacity, and overall prognosis in transplant recipients [42].

The association between higher educational attainment and cognitive improvement post-transplant is consistent with the cognitive reserve hypothesis, which posits that individuals with greater lifelong cognitive engagement - often reflected by formal education - may be more resilient to the effects of brain injury, including those related to hepatic encephalopathy. Although the current sample size is limited, the statistically significant difference in education between improved and declined patients lends further support to this concept.

Notably, age did not significantly differentiate outcome groups, suggesting that within this cohort, cognitive reserve may have been a more relevant determinant of cognitive recovery than chronological age.

Future studies should aim to incorporate neuroimaging and biomarkers to elucidate the mechanisms underlying CI. Clinical trials of cognitive training and pharmacologic interventions in this population are also needed to guide individualized care strategies.

Limitations

This study has several limitations. First, data on the duration and quantity of alcohol consumption were not collected. However, all patients had abstained from alcohol for at least 6 months, verified by psychiatric assessment. Second, DSM-5 criteria were not applied to diagnose major or minor neurocognitive disorders. Nonetheless, ACE-III testing was performed by a psychiatrist during standard pre-transplant evaluation, following exclusion of major neurological conditions via MRI. Third, minimal hepatic encephalopathy was not assessed using tools such as the MMSE due to the pilot nature of the study.

Additionally, comparing our findings with previous research is challenging due to variability in study populations, methodologies, and sample sizes. Despite these limitations, our study provides important data from a relatively large, etiologically homogeneous cohort of AUD-related ESLD patients, showing a disturbingly high prevalence of CI. Routine cognitive screening may facilitate earlier interventions and improved clinical management.

CONCLUSION

This study demonstrates a concerning prevalence of severe cognitive impairment, potentially indicative of dementia, in patients with alcohol-related ESLD both before and after liver transplantation. Although most patients showed post-transplant improvement, persistent deficits in memory and language highlight the need for ongoing monitoring. Our findings support routine cognitive screening in this population and underscore the importance of further research into predictive markers and therapeutic interventions aimed at preserving and enhancing cognitive function after LT.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving humans were approved by the BioethicsCommittee of the Medical University of Warsaw (approval number KB/81/2022). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG-S and PO - data collection. MJ - statistical analysis, manuscript revision. JR-W, AG, JM - concept, data processing. MG-S, MJ, JR-W - manuscript preparation. MG-S, MJ, PO, AG, JM, JR-W - revision and approval of the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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AHEAD OF PRINT

Cognitive impairment in liver transplant candidates: The role of blood ammonia level and three-point evaluation of brain MRI

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Abstract

Background. Cognitive impairment (CI) is common in patients with alcohol-use disorder (AUD)-related liver cirrhosis, especially those awaiting liver transplantation (LT). There are conflicting results in terms of the role of hepatic encephalopathy (HE) in CI development and persistence.

Objectives. This study investigated the impact of hyperammonemia on CI and evaluated the role of routine magnetic resonance imaging (MRI) in detecting CI among patients with AUD-related cirrhosis listed for LT at a single center.

Materials and methods. Fifty-two adults (36 males, 69%) with AUD-related liver cirrhosis (mean age: 51 ±11 years; mean Model for End-Stage Liver Disease (MELD) score 16 ±6) were evaluated. Cognitive function was assessed using the Addenbrooke's Cognitive Examination III (ACE-III), with scores below 82 indicating probable dementia. Magnetic resonance imaging evaluations focused on cortical-subcortical atrophy, vascular-origin changes and chronic HE.

Results. Magnetic resonance imaging revealed HE-related changes in 38 patients (73%), vascular-origin changes in 32 patients (62%) and cortical-subcortical atrophy in 15 patients (29%). Cognitive impairment was present in 46 patients (88%), with 30 (58%) suspected of having dementia. Patients with MRI evidence of HE scored lower in the ACE III language subdomain ($p = 0.032$) and tended toward a higher Child–Pugh classification ($p = 0.083$). No significant differences were found in ACE-III results or clinical data between patients with and without vascular-origin changes or cortical–subcortical atrophy. Additionally, no correlations were observed between radiological findings, ammonia levels, ACE-III scores, and liver-related mortality.

Conclusions. These findings reveal a high prevalence of CI and significant MRI abnormalities in AUD patients awaiting LT. Further studies are needed to clarify the role of routine MRI in detecting cognitive deficits.

Key words: cognitive impairment, liver transplantation, brain magnetic resonance, alcohol-related liver cirrhosis, blood ammonia level

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Highlights

- Cognitive impairment was detected in 88% of AUD-related cirrhosis patients awaiting liver transplantation. Routine MRI showed brain atrophy or vascular changes in over 60% of candidates.
- No MRI features or ammonia levels significantly predicted cognitive performance.
- Liver functional reserve (Child-Pugh score) showed a non-significant trend with cognitive decline.

Background

Alcohol-use disorder (AUD), as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), encompasses maladaptive patterns of alcohol use that lead to significant clinical consequences.[1] Chronic alcohol consumption often leads to liver cirrhosis, one of the primary indications for liver transplantation (LT).[2,3] Hepatic encephalopathy (HE), a severe neuropsychiatric syndrome associated with liver cirrhosis, arises from elevated ammonia and inflammation, resulting in low-grade cerebral edema, oxidative/nitrosative stress, inflammation, and disrupted brain oscillatory networks.[4] While blood ammonia serves as a biomarker with good negative predictive value for HE,[5,6] alcohol independently causes neurotoxic effects, damaging brain regions such as the frontal lobe, cerebellum and limbic system, including the hippocampus,[7,8] which further impairs brain function. Thus, chronic alcohol use and liver dysfunction are clearly linked to cognitive impairment (CI), likely through disruption of frontal–subcortical circuits and associated neurotransmitter imbalances.

Patients with liver cirrhosis commonly experience CI before LT, with recovery post-transplant varying in extent and timeline.[9,10] The history of HE appears to influence post-transplant recovery of brain function and connectivity.[8] Various factors, including minimal and overt HE, chronic alcohol use and gut microbial dysbiosis, contribute to CIs in cirrhosis, with prolonged alcohol use associated with severe deficits in executive function, attention, motor skills, spatial reasoning, language, and memory.[11,12] Alcohol-induced neuroinflammation further reduces hippocampal white matter and prefrontal cortex volume, impairing memory and decision-making abilities.[7,13] Magnetic resonance imaging (MRI) remains a valuable tool for monitoring brain changes and evaluating recovery potential after transplantation, underscoring its importance in elucidating the neurobiological basis of CI in alcohol-related liver disease (ALD) and HE. Despite its clinical importance, detailed analysis of brain MRI findings is not readily available in routine practice.

In ALD, chronic alcohol consumption leads to significant cognitive deficits, particularly in executive function, memory and attention, through neurotoxic effects that disrupt glutamate and GABA neurotransmitter balance and impair the frontal–subcortical circuits essential for cognitive processing and behavioral regulation.[13] Alcohol also induces brain inflammation and oxidative stress, leading to structural and functional alterations. MRI studies show that patients with ALD often exhibit reduced gray matter in the frontal cortex and subcortical regions, changes that correlate with cognitive decline and increased susceptibility to HE.[13]

In HE, elevated ammonia disrupts astrocyte function, leading to increased glutamine levels, astrocyte swelling and cerebral edema.[13] These changes impair neurotransmitter metabolism, manifesting as deficits in attention, reaction time and executive function. Hepatic encelopathy-related CI is associated with MRI abnormalities in the basal ganglia due to manganese deposition from chronic liver disease.[14] Ammonia accumulation also disrupts dopaminergic, glutamatergic and serotonergic pathways, further affecting frontal–subcortical circuits critical for cognitive processing.[14,15]

The MRI findings in HE patients frequently show basal ganglia abnormalities and cerebral edema, likely from astrocyte swelling and metabolic disruptions.[14,15] Even after transplantation, cognitive impairments, particularly in attention and executive function, often persist and are associated with reduced volumes in the frontal lobe and basal ganglia.[14,15] Cognitive deficits in ALD and HE primarily result from disruptions in frontal–subcortical circuits caused by alcohol-induced dysregulation of glutamate and GABA, compounded by the neurotoxic effects of ammonia, as noted above. Ammonia also damages astrocytes, which are essential for detoxification and neurotransmitter balance, further impairing neural communication between the basal ganglia and frontal cortex.[15] The impact of ammonia on astrocyte function underscores the need for early intervention to prevent cognitive decline in LT candidates.

Objectives

This study examines the predictive value of 3-point routine brain MRI evaluations for cognitive impairment in consecutive liver transplant candidates with alcohol use disorder-related liver cirrhosis at a single transplant center.

Materials and methods

Participants

A total of 52 adult patients (69% male, comprising 36 men and 16 women) with a mean age of 51 ±11 years, all diagnosed with AUD-related liver cirrhosis, were identified as potential candidates for LT in a single liver transplant center. The mean Model for End-Stage Liver Disease (MELD) score was 16 ±6, indicating an advanced stage of liver disease in the study cohort. The main indication for LT assessment in AUD patients was chronic liver failure (87%). However, 13% of patients had hepatocellular carcinoma (HCC) as the indication for LT.

Study design

All patients included in this cross-sectional single-center study were admitted in 2023 to the Department of Hepatology, Transplantology and Internal Medicine of the Medical University of Warsaw (Poland), to work-up for listing to LT, including biochemical and serological testing and cardiology, pulmonology and imaging studies, including brain MRI. The exclusion criteria included regular intake of hypnotics, severe overt HE and psychiatric or neurodegenerative diseases, making it impossible to perform the investigation. Blood ammonia levels were routinely measured as part of the laboratory work-up for all participants.

Cognitive assessment

Cognitive function was assessed using the Addenbrooke Cognitive Examination III (ACE III), which is a comprehensive tool designed to detect CI across various domains. A cutoff score of less than 82 on the ACE III was utilized to identify patients with a high likelihood of dementia. The ACE III covers cognitive domains such as attention, memory, verbal fluency, language, and visuospatial abilities. The Polish version is available free of charge.[16] The ACE-III has been previously validated against standard neuropsychological tests. In addition, our center has prior experience with this tool, reflected in previously published projects.[18,19] All patients were routinely examined during their stay in the hospital by a psychiatrist dedicated to the transplant program, according to the pre-transplant work-up protocol, which consists of full psychiatric consultation, as well as the ACE III tool. The "liver-related mortality" was defined as a death occurring during the study.

Magnetic resonance imaging evaluation

Each patient underwent brain MRI using Siemens Magnetom Avanto 1.5T (Siemens AG, Erlangen, Germany) as part of their routine pre-transplant assessment. The MRI scans were evaluated using a standardized 3-point approach, focusing on the assessment of cortical-subcortical atrophy, a semi-quantitative evaluation of vascular-related changes, and the identification of features consistent with chronic HE. All MRI images were analyzed by experienced radiologists blinded to the cognitive functions assessment results and venous blood ammonia level. Organic brain changes in MRI, including cortical-subcortical atrophy, vascular-origin alterations and HE-related abnormalities, were systematically assessed and described using the Fazekas scale to ensure clarity and reproducibility. The results from these MRI scans were then correlated with cognitive test scores and clinical parameters.

Blood ammonia measurement

Venous blood was collected from all subjects (fasting) for the assessment of blood ammonia concentration, which was measured in ethylenediaminetetraacetic acid (EDTA) plasma using the enzymatic method with glutamate dehydrogenase (GLDH) on Dimension EXL (Siemens Healthineers, Forchheim, Germany). Reference values were 19–55 μg/dL.

Ethics

Appropriate informed consent was obtained from each patient included in the study. The study protocol was approved by the Bioethics Committee of the Medical University of Warsaw (approval No. KB/81/2022 and amendment No. KB42/A 2025) and was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008).

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics v. 29.0 (IBM Corp., Armonk, USA) and Python v. 3.10 (https://www.python.org/downloads/release/python-3100; SciPy and StatsModels packages) for advanced corrections. The normality of continuous variables was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Due to the non-normal distribution of key variables, including MELD, ACE III scores, and blood ammonia levels, nonparametric tests were applied for both group comparisons and correlation analyses.

Continuous variables are presented as median (Q1–Q3) for non-normally distributed data and as mean ± standard deviation (SD) when normally distributed. Categorical variables are expressed as absolute numbers and percentages.

Group comparisons between patients with positive (ACE III < 82) and negative screening results were conducted using the Mann–Whitney U test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables, depending on expected cell frequencies. The χ^2 test assumptions were verified by calculating expected frequencies, which are presented in the Supplementary Table 1 (https://doi.org/10.5281/zenodo.17104342).

Correlations were evaluated using Spearman's rank correlation coefficient due to the nonparametric nature of the data. The analyses examined associations between MRI features (HE signs, vascular-origin changes and cortical–subcortical atrophy) and ACE-III total and domain scores; clinical parameters (Child–Pugh score, MELD score and blood ammonia) and cognitive function; and ACE-III total scores and both radiological features and clinical variables.

To control for multiple comparisons, the Benjamini–Hochberg false discovery rate (FDR) correction was applied across all sets of correlation analyses and group comparisons involving multiple variables. This method was chosen over Bonferroni to maintain statistical power while limiting false discoveries in an exploratory context.

Statistical results are reported with appropriate test statistics (U, χ^2, r), degrees of freedom where relevant and p-values rounded to 3 decimal places. The p-values less than 0.001 are reported as $p < 0.001$. An FDR-corrected $p < 0.05$ was considered statistically significant, and such results are marked with an asterisk in the tables.

Results

The clinical characteristics of the study cohort are summarized in Table 1. The median Model of End-Stage Liver Disease-Sodium (MELD-Na) score was 16 (Q1–Q3: 12–19) points, while the median Child–Pugh score was 8 (7–9) points. The median venous blood ammonia concentration was 83.5 µg/dL (Q1–Q3: 53–108), with 24 patients (46%) showing hyperammonemia, defined as > 55 µg/dL.

The median ACE III score across the entire cohort was 79 points (Q1–Q3: 69–88); 46 patients (88%) displayed impaired cognitive performance, as indicated by an ACE III score below 89 points, and 30 patients (58%) met the criteria for high probability of dementia, defined by an ACE III score below 82 points.

Radiological signs consistent with HE were observed in brain MRI scans of 38 patients (73%). These patients did not significantly differ from others in terms of age, sex, venous blood ammonia levels, MELD-Na scores, or total ACE III results (Mann–Whitney U test or Pearson's χ^2 test; all FDR-corrected $p > 0.05$). Although the uncorrected analysis showed lower language domain scores in patients with radiological signs of HE ($U = 207.5$, $p = 0.032$), this association was no longer significant after correction for multiple comparisons (FDR-adjusted $p = 0.067$). Similarly, a trend toward higher Child–Pugh classifications in these patients ($U = 338.5$, uncorrected $p = 0.083$) did not reach statistical significance after FDR correction.

Spearman's correlation analyses revealed no statistically significant associations, after correction for multiple comparisons, between any of the evaluated MRI features (HE, vascular-origin changes, cortical–subcortical atrophy) and ACE III total or domain scores. Full results are presented in Table 2.

Vascular-origin changes were reported in 32 patients (62%). Uncorrected comparisons showed a significant association with lower total ACE III scores (χ^2 test, $p = 0.045$), but this finding was not significant after FDR correction (adjusted $p = 0.090$). No associations were found between vascular-origin changes and clinical variables or hyperammonemia (FDR-adjusted $p > 0.05$).

Cortical–subcortical atrophy was identified in MRI scans of 15 patients (29%). Uncorrected analyses showed an association between atrophy and CI (χ^2 test, $p = 0.038$), but this finding did not remain significant after FDR correction (adjusted $p = 0.081$). No significant relationships were observed between cortical-subcortical atrophy and age, sex, ammonia levels (quantitative or categorical), MELD-Na, or Child–Pugh scores.

Table 1. Clinical characteristics of the study cohort and the subgroups of patients with positive and negative screening in ACE III Test for dementia (i.e., <82 points) in relation to demographic, clinical and imaging results

Variable	Total cohort (n = 52)	ACE III < 82 (n = 30)	ACE III ≥ 82 (n = 22)	Statistical test	Test statistic	p-value	FDR-corrected p-value
Age [years]	51.0 (44.0–59.0)	55.0 (44.5–59.0)	49.5 (43.8–54.5)	Mann–Whitney U	374.000	0.420	0.864
Gender (male %)	0 (0%)	0 (0%)	0 (0%)	Fisher's Exact	0.918	1.000	1.000
MELD score	15.0 (11.0–20.2)	16.0 (12.2–20.8)	13.0 (10.2–20.0)	Mann–Whitney U	370.000	0.463	0.864
Child–Pugh score	8.0 (7.0–10.0)	8.0 (7.2–11.0)	8.5 (6.0–9.8)	Mann–Whitney U	398.500	0.202	0.864
Blood ammonia [µg/dL]	73.0 (52.1–123.9)	80.2 (55.1–129.6)	64.3 (51.3–89.0)	Mann–Whitney U	370.000	0.464	0.864
MRI: signs of hepatic encephalopathy	38 (73%)	23 (77%)	15 (68%)	Fisher's Exact	0.652	0.540	0.864
MRI: vascular-origin changes	52 (100%)	30 (100%)	22 (100%)	χ^2	0.000	1.000	1.000
MRI: cortical-subcortical atrophy	52 (100%)	30 (100%)	22 (100%)	χ^2	0.000	1.000	1.000

All p-values were calculated using the Mann–Whitney U test or Fisher's exact test, where appropriate. False discovery rate (FDR) correction was applied using the Benjamini–Hochberg method. ACE III – Addenbrooke Cognitive Test III; HE – hepatic encephalopathy; MELD – Model of End-Stage Liver Disease; MRI – magnetic resonance imaging.

Table 2. Correlations between impairments in MRI of the brain and domains of The Addenbrooke Cognitive Test III in liver transplant recipients

MRI feature	ACE III domain	Spearman's r	p-value	n	FDR-corrected p-value
MRI: signs of hepatic encephalopathy	ACE III total	−0.169	0.231	52	0.655
MRI: signs of hepatic encephalopathy	Attention	−0.182	0.196	52	0.655
MRI: signs of hepatic encephalopathy	Memory	−0.009	0.951	52	0.951
MRI: signs of hepatic encephalopathy	Fluency	−0.096	0.498	52	0.748
MRI: signs of hepatic encephalopathy	Language	−0.299	0.032	52	0.555
MRI: signs of hepatic encephalopathy	Visuo-spatial abilities	−0.236	0.093	52	0.555
MRI: vascular-origin changes	ACE III Total	0.049	0.731	52	0.802
MRI: vascular-origin changes	Attention	0.258	0.065	52	0.555
MRI: vascular-origin changes	Memory	0.149	0.291	52	0.655
MRI: vascular-origin changes	Fluency	−0.11	0.437	52	0.748
MRI: vascular-origin changes	Language	0.064	0.652	52	0.782
MRI: vascular-origin changes	Visuo-spatial abilities	0.126	0.373	52	0.747
MRI: cortical-subcortical atrophy	ACE III Total	0.096	0.497	52	0.748
MRI: cortical-subcortical atrophy	Attention	0.074	0.603	52	0.775
MRI: cortical-subcortical atrophy	Memory	−0.044	0.757	52	0.802
MRI: cortical-subcortical atrophy	Fluency	0.08	0.574	52	0.775
MRI: cortical-subcortical atrophy	Language	0.198	0.16	52	0.655
MRI: cortical-subcortical atrophy	Visuo-spatial abilities	0.157	0.267	52	0.655

Spearman's rank correlation was used to assess the association between MRI features and cognitive test performance (ACE III total and domain scores). The p-values were corrected for multiple comparisons using the Benjamini–Hochberg False Discovery Rate (FDR) method. ACE III – Addenbrooke Cognitive Test III; HE – hepatic encephalopathy; MELD – Model of End-Stage Liver Disease; MRI – magnetic resonance imaging; *FDR-corrected $p < 0.05$.

Table 3. The correlations of ACE III total score and its domains with Child–Pugh Score, MELD-Na Score, and venous ammonia levels

Row type	Variable	ACE III	Attention	Memory	Fluency	Langugage	Visuo-spatial abilities
Spearman's r	Child–Pugh score	−0.283	−0.443*	−0.053	−0.223	−0.433*	−0.282
Spearman's r	MELD-Na score	−0.093	−0.226	0.045	−0.1	−0.222	−0.109
Spearman's r	venous ammonia level	−0.127	−0.243	−0.083	−0.076	−0.094	−0.247
p-value (FDR corrected)	Child–Pugh score	0.194	0.0123	0.753	0.226	0.0123	0.194
p-value (FDR corrected)	MELD-Na score	0.659	0.226	0.753	0.659	0.226	0.659
p-value (FDR corrected)	venous ammonia level	0.659	0.226	0.669	0.669	0.659	0.226

Spearman's rank correlation was used to assess associations between clinical parameters and ACE III total and domain scores; p-values were corrected for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) method. ACE III – Addenbrooke Cognitive Test III; HE – hepatic encephalopathy; MELD – Model of End-Stage Liver Disease; MRI – magnetic resonance imaging. *FDR-corrected p-values < 0.05.

Table 3 presents the correlations between ACE III total and domain scores with clinical parameters, including blood ammonia, MELD-Na, and Child–Pugh scores. No significant correlations were observed between ammonia or MELD-Na and cognitive performance (Spearman's r, all FDR-adjusted $p > 0.05$). While uncorrected correlations suggested a relationship between Child–Pugh scores and ACE III total, attention, language, and visuospatial abilities, none of these remained significant after FDR correction. Scatterplots illustrating selected relationships between cognitive domains and clinical/imaging features are presented in Fig. 1.

Five patients (9.6%) died during the study period, all following liver transplantation due to infection and/or surgical complications. No significant differences in mortality were found between patients with or without radiological signs of HE, vascular-origin changes or cortical-subcortical atrophy, nor between CI groups (ACE III < 82 vs ≥ 82) (Pearson's χ^2 test, all $p > 0.05$).

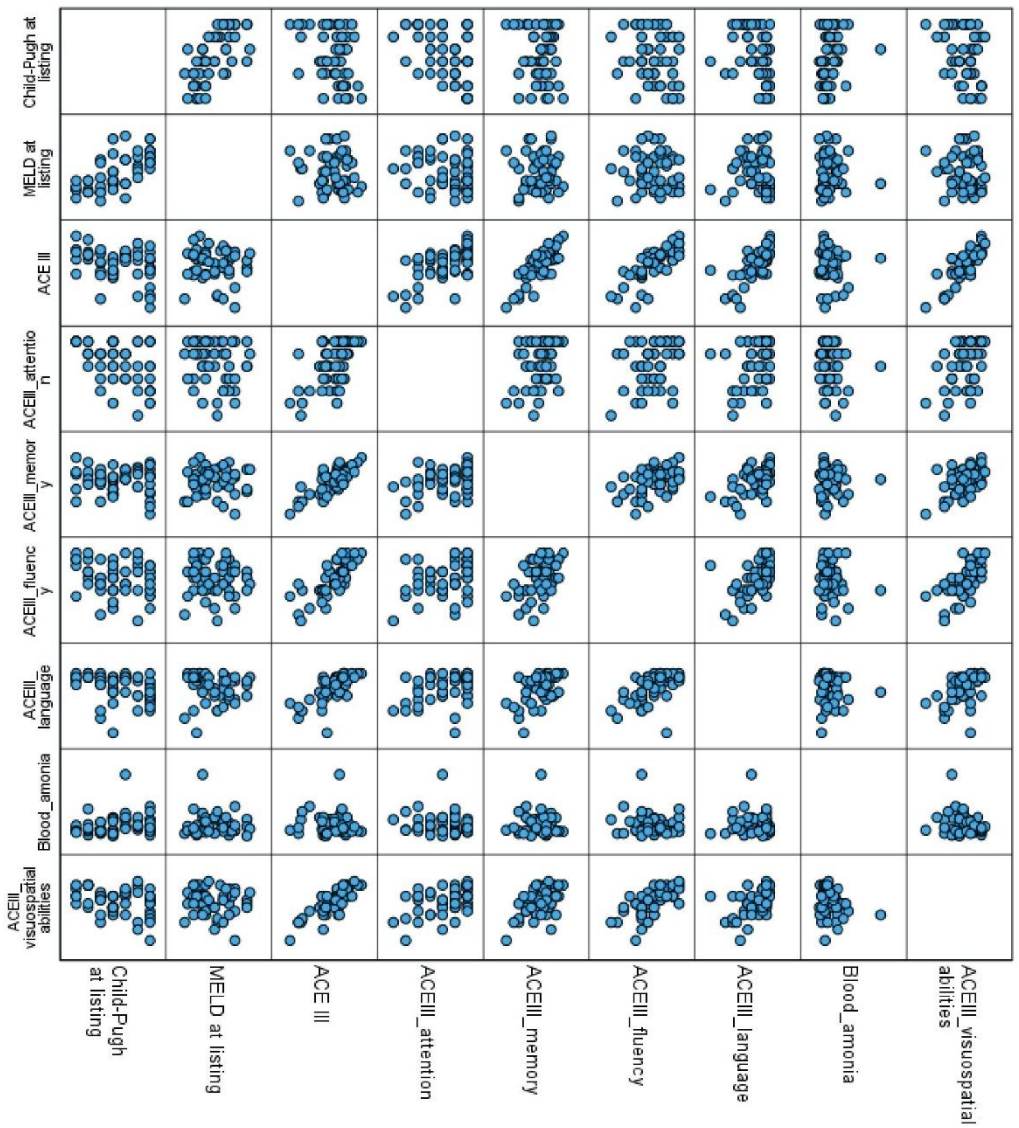

Fig. 1. Scatterplots illustrating the relationship between variables tested with Spearman's rank correlation coefficient

Discussion

The findings from this study confirm a high prevalence of CI among liver transplant candidates with end-stage liver disease (ESLD) related to AUD. This homogeneous cohort of AUD patients revealed a concerning frequency of structural brain changes on routine MRI. While numerous studies have investigated cognitive dysfunction in patients with hepatitis C and non-alcoholic fatty liver disease (NAFLD) using advanced imaging techniques (e.g., magnetic resonance spectroscopy (MRS), functional MRI,[20–22] such tools remain largely unavailable in routine pre-transplant care. Most standard clinical brain MRI reports do not include quantitative metrics such as mean diffusivity or fractional anisotropy.[23,24] Therefore, our study underscores the value of assessing cognitively vulnerable

ESLD patients using accessible and widely available neuroimaging tools.

Our data showed that vascular-origin changes and cortical-subcortical atrophy were frequent, even in a relatively young population (mean age: 51 years). Additionally, a striking proportion of patients demonstrated moderate-to-severe CI, with more than half meeting criteria for high dementia probability based on ACE III. This level of dysfunction may impact transplant candidacy through impaired treatment adherence and increased post-transplant risks, including graft rejection.[10]

Contrary to our initial assumptions, no significant correlations were found between radiological features and cognitive test scores after correction for multiple comparisons. Although patients with signs of HE showed lower scores in the language domain of the ACE III in uncorrected analysis, this finding did not remain statistically significant following FDR adjustment. Similarly, no MRI feature (including vascular-origin changes and atrophy) was significantly associated with cognitive performance in domain-level correlations.

These findings align with the growing understanding that blood ammonia levels, often central to the HE narrative, are unreliable markers of cognitive status in ESLD.[4–6] Our study confirms that ammonia levels were not correlated with ACE III total or domain scores, reinforcing the notion that multiple metabolic and systemic variables confound its interpretation.[25]

Contributing factors include individual variation in urea cycle function, dietary protein intake and hydration status, all of which can affect ammonia levels without reflecting cognitive decline. Additionally, limited access to anti-ammonia therapies (e.g., lactulose, rifaximin), whether due to cost constraints or poor adherence, may further confound this relationship in real-world settings.

The role of HE in long-term CI remains debated. Although LT improves ammonia clearance, persistent deficits post-transplantation have been widely reported.[12,26] Some studies suggest that structural brain damage from prior HE episodes may be irreversible,[9,27] whereas others report partial reversal of MRI abnormalities after transplantation.[28] Notably, Bajaj et al.[29] found that episodes of overt HE led to persistent deficits in working memory and response inhibition. Similarly, studies by Adejumo et al.[30] and Lopez-Franco et al.[31] point to a relationship between HE and dementia that may persist beyond the transplant period. However, evidence remains conflicting. While Ko et al.[32] did not find a clear link between pre- and post-transplant cognition, Berry et al.[33] highlighted pre-transplant CI as the strongest predictor of post-transplant dysfunction. Cheng et al.[34] demonstrated persistent abnormalities in functional brain connectivity in patients with prior HE, especially in regions responsible for higher-order cognition.

Our analysis identified a consistent, though uncorrected, association between cognitive performance and liver functional reserve, particularly the Child–Pugh score. This aligns with known links between advanced liver dysfunction, metabolic alterations and cognitive deficits.[35,36] However, after FDR correction, these associations lost statistical significance, suggesting the need for cautious interpretation. The trend may reflect the combined impact of malnutrition, systemic inflammation and energy metabolism deficits.[11,37]

The MELD score, which does not account for albumin or nutritional status, was not related to cognitive outcomes. This discrepancy further supports the theory that chronic nutritional deficits, captured in part by the Child–Pugh classification, may be more relevant in assessing cognitive vulnerability in this population. The high prevalence of CI in our ESLD cohort also exceeds that reported in kidney transplant recipients.[38]

Limitations

This single-center study addressed a critical gap in transplantology by focusing on AUD patients with ESLD – a clinically uniform group often underrepresented in cognitive research. Nevertheless, the sample size limits generalizability, and the lack of comprehensive neuropsychological testing or DSM-5-based diagnoses precludes a definitive classification of cognitive disorders.

While the ACE III is a robust screening tool, it cannot replace a detailed diagnostic evaluation. Additionally, the cross-sectional design prevents inferences regarding the trajectory of cognitive dysfunction, either pre- or post-transplant. Further studies should explore how routine MRI findings relate to post-LT outcomes, particularly in the presence or absence of HE history.

Conclusions

This study confirms the high prevalence of CI among liver transplant candidates with ESLD. Although structural brain abnormalities were frequently observed, they were not significantly associated with cognitive test outcomes after adjustment for multiple comparisons. Similarly, blood ammonia levels did not predict cognitive function.

Although subtle trends were observed between the Child–Pugh score and ACE III performance, these did not reach statistical significance after FDR correction. Our findings support growing evidence that cognitive dysfunction in ESLD may be multifactorial, involving metabolic, nutritional and neuroinflammatory pathways beyond hyperammonemia alone. Future research should aim to refine neuroimaging biomarkers and integrate broader systemic assessments to better characterize cognitive risk in this vulnerable population.

Supplementary data

The supplementary materials are available at https://doi.org/10.5281/zenodo.17104342. The package includes the following files:

Supplementary Table 1. Expected frequencies for categorical variables analyzed with the χ^2 test.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable

Use of AI and AI-assisted technologies

During the preparation of this work the authors used Chat GPT in order to improve language and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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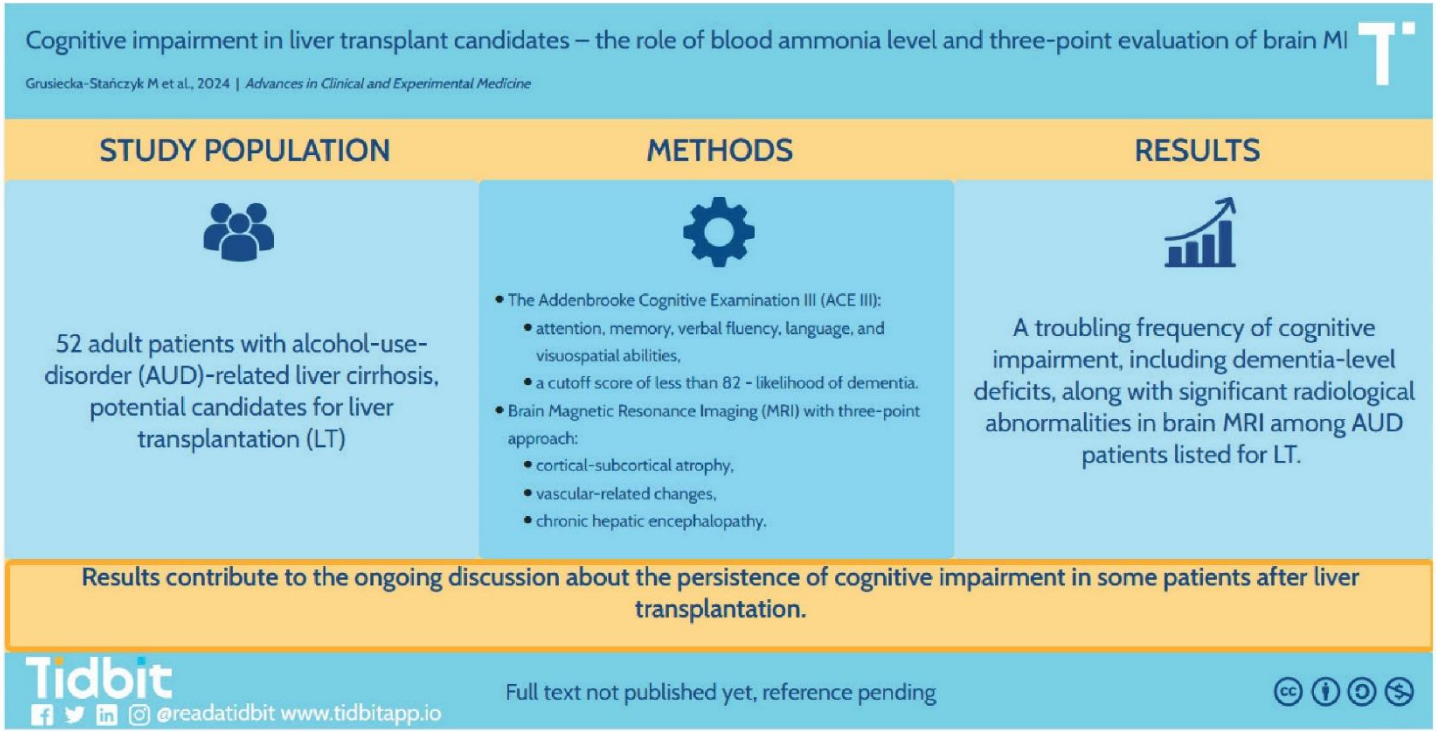
Graphical abstract



Podsumowanie i wnioski

Przeprowadzony cykl trzech badań stanowi pierwszą w literaturze próbę całościowego i konsekwentnego ujęcia problemu zaburzeń poznawczych u pacjentów z alkoholową chorobą wątroby (ALD) w kontekście transplantacji wątroby. Zastosowanie jednorodnej kohorty chorych pozwoliło na uzyskanie wiarygodnych, klinicznie istotnych wyników, które wypełniają istotną lukę w dotychczasowych badaniach prowadzonych w grupach mieszanych etiologicznie.

Pierwsza publikacja (nr 1) zidentyfikowała szczególne narażenie pacjentów z ALD na deficyty poznawcze. W bezpośrednim porównaniu z chorymi oczekującymi na przeszczepienie nerki, kandydaci do transplantacji wątroby uzyskali istotnie gorsze wyniki testu ACE-III: 70,9 vs 91,6 pkt, a częstość rozpoznawania CI była kilkukrotnie wyższa (90% vs 26%). Wynik ten jednoznacznie wskazał, że ALD wiąże się z wyjątkowo dużym obciążeniem poznawczym, wykraczającym poza niespecyficzne skutki przewlekłej choroby narządowej.

Druga publikacja (nr 2) rozszerzyła analizę na okres po transplantacji wątroby, oceniając dynamikę zmian funkcji poznawczych. W badanej kohorcie aż 86% pacjentów miało upośledzenie funkcji poznawczych przed transplantacją wątroby, z czego znaczna część spełniała kryteria wysokiego ryzyka otępienia. Po przeszczepieniu wątroby obserwowano częściową poprawę w wybranych domenach (pamięć, płynność słowna, funkcje przestrzenne), ale jednocześnie deficyty nie były w pełni odwracalne, a w niektórych obszarach (język) dochodziło nawet do pogorszenia. To kluczowa obserwacja kliniczna, pokazująca, że transplantacja nie eliminuje całkowicie zaburzeń poznawczych, a pacjenci z ALD wymagają dalszego monitorowania neuropsychologicznego także po zabiegu.

Trzecia publikacja (nr 3) dopełniła cykl analizą możliwych mechanizmów CI u chorych z ALD z wykorzystaniem neuroobrazowania rezonansowego mózgowia. W badaniach nie stwierdzono jednoznacznej zależności między poziomem amoniaku, obrazem MRI encefalopatii wątrobowej a nasileniem deficytów poznawczych. Oznacza to, że klasyczne biomarkery, dotychczas uznawane za kluczowe w patogenezie encefalopatii wątrobowej, nie tłumaczą w pełni zjawiska CI w tej grupie. Wynik ten otwiera nowe perspektywy badawcze, sugerując złożoną, wieloczynnikową etiologię zaburzeń.

Łącznie, cykl badań pozwala na całościową charakterystykę problemu: od poznania częstości występowania zaburzeń poznawczych, przez ocenę dynamiki zmian w następstwie transplantacji, po próbę wyjaśnienia mechanizmów patofizjologicznych. Wyniki jednoznacznie

wskazują, że pacjenci z ALD powinni być traktowani jako grupa szczególnego nadzoru poznawczego. Konieczne jest wdrożenie systematycznej oceny neuropsychologicznej zarówno w okresie kwalifikacji, jak i w obserwacji pooperacyjnej, a także opracowanie programów długoterminowego wsparcia kognitywnego.

Opinia Komisji Bioetycznej

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
Fax: 022/ 57 - 20 -165

ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

KB/ 42 /A 2025

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 08 września 2025 r. po zapoznaniu się z wnioskiem:

Dr hab. n.med. Aleksandra Golenia,
Klinika Neurologii ,
ul. Banacha 1a, 02-097 Warszawa

dotyczącym: akceptacji dokumentacji obejmujących:
-Zmianę tytułu badania z „ Zaburzenia funkcji poznawczych u pacjentów chorych na przewlekłą chorobę nerek i po przeszczepie wątroby." na „Zaburzenia funkcji poznawczych u pacjentów przed i po przeszczepieniu nerki oraz przed i po transplantacji wątroby."
-Program badania wersja 2 z dnia 05.08.2025 r (rozszerzenie grupy badanej)

wyraża następującą
o p i n i ę

- stwierdza, że są one dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że są one niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

-Komisja działa na podstawie regulaminu działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym, przyjętego zarządzeniem Rektora WUM nr 200/2022 z dnia 18 października 2022 r. oraz przepisów prawa powszechnie obowiązującego, w tym przede wszystkim ustawy z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty, ustawy z dnia 6 września 2001 r. Prawo farmaceutyczne, ustawy z 22 kwietnia 2022 r. o wyrobach medycznych oraz prawa międzynarodowego lub unijnego, a także odpowiednich norm naukowych lub zawodowych.

Przewodniczący Komisji Bioetycznej

Prof. dr hab. n.med. Magdalena Kuźma-Kozakiewicz

*niepotrzebne skreślić

Komisja Bioetyczna
przy Warszawskim Uniwersytecie Medycznym

Tel.: 022/ 57 - 20 -303
Fax: 022/ 57 - 20 -165

ul. Żwirki i Wigury nr 61
02-091 Warszawa

e-mail: komisja.bioetyczna@wum.edu.pl
www.komisja-bioetyczna.wum.edu.pl

KB/..81../2022

Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym
w dniu 13 czerwca 2022 r. po zapoznaniu się z wnioskiem

Dr n.med. Aleksandra Golenia
Katedra i Klinika Neurologii,
ul. Banacha 1A, 02-097 Warszawa

dotyczącym: wyrażenia opinii w sprawie badania pt." Zaburzenia funkcji poznawczych u pacjentów chorych na przewlekłą chorobę nerek i po przeszczepie wątroby."

- Badanie może być prowadzone wyłącznie w okresie obowiązywania polisy ubezpieczeniowej.

wyraża następującą
o p i n i ę

- stwierdza, że jest ono dopuszczalne i zgodne z zasadami naukowo-etycznymi*.
- ~~stwierdza, że jest ono niedopuszczalne i niezgodne z zasadami naukowo-etycznymi.*~~

Uwagi Komisji – ***verte***

Komisja działa na podstawie art.29 ustawy z dnia 5.12.1996r. o zawodzie lekarza /Dz.U.nr 28/97 poz.152 wraz z późn.zm./, zarządzenia MZiOS z dn.11.05.1999r. w sprawie szczegółowych zasad powoływania i finansowania oraz trybu działania komisji bioetycznych /Dz.U.nr 47 poz.480/, Ustawy prawo farmaceutyczne z dnia 6 września 2001r. (Dz.U.Nr 126, poz. 1381 z późn. zm.) oraz Zarządzenie nr 56/2007 z dnia 15 października 2007r. w sprawie działania Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym /Regulamin Komisji Bioetycznej przy Warszawskim Uniwersytecie Medycznym/.
Komisja działa zgodnie z zasadami GCP .

Przewodnicząca Komisji Bioetycznej

Prof. dr hab. n. med. Magdalena Kuźma-Kozakiewicz

*niepotrzebne skreślić

Oświadczenie współautorów publikacji

Warszawa, 19.09.2025

(miejscowość, data)

Dr hab. n. med. Aleksandra Golenia

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive impairment in patients awaiting kidney and liver transplantation - A clinically relevant problem? Brain Behav. 2024 Aug;14(8): e3647.doi: 10.1002/brb3.3647, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: opracowanie koncepcji badania i zaprojektowanie jego metodologii, analiza i interpretacja danych, przygotowanie manuskryptu (20%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

Aleksandra Golenia

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Piotr Olejnik

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive impairment in patients awaiting kidney and liver transplantation - A clinically relevant problem? Brain Behav. 2024 Aug;14(8): e3647.doi: 10.1002/brb3.3647, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zbieranie danych i ich gromadzenie (5%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

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(imię i nazwisko kandydata do stopnia)

Piotr Olejnik

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(podpis oświadczającego)

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Warszawa, 19.09.2025

(miejscowość, data)

Jolanta Małyszko

(imię i nazwisko)

OŚWIADCZENIE

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Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

Prof. dr hab. Jolanta Małysz
specjalista nefrolog
hipertensjolog, transplantolog kliniczn
choroby wewnętrzne
3365446

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Paweł Żebrowski

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive impairment in patients awaiting kidney and liver transplantation - A clinically relevant problem? Brain Behav. 2024 Aug;14(8): e3647.doi: 10.1002/brb3.3647, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zbieranie danych (5%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu.

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Joanna Raszeja-Wyszomirska

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive impairment in patients awaiting kidney and liver transplantation - A clinically relevant problem? Brain Behav. 2024 Aug;14(8): e3647.doi: 10.1002/brb3.3647, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: nadzór merytoryczny i przegląd literatury (5%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (50%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

Prof. dr hab. n. med. Joanna Raszeja-Wyszomirska
specjalista chorób wewnętrznych
i transplantologii klinicznej
3176900

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Maciej Janik

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive impairment in liver transplant candidates: the role of blood ammonia level and three-point evaluation of brain MRI. Adv Clin Exp Med. 2026;35(2). doi:10.17219/acem/204837, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: analiza statystyczna uzyskanych wyników (7.5%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (60%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

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(podpis oświadczającego)

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Warszawa, 19.09.2025

(miejscowość, data)

Aleksandra Golenia

(imię i nazwisko)

OŚWIADCZENIE

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Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (60%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

Aleksandra Golenia

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Piotr Olejnik

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive impairment in liver transplant candidates: the role of blood ammonia level and three-point evaluation of brain MRI. Adv Clin Exp Med. 2026;35(2). doi:10.17219/acem/204837, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zbieranie i gromadzenie danych (7.5%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (60%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

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Piotr Olejnik

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Warszawa, 19.09.2025

(miejscowość, data)

Jolanta Małyszko

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive impairment in liver transplant candidates: the role of blood ammonia level and three-point evaluation of brain MRI. Adv Clin Exp Med. 2026;35(2). doi:10.17219/acem/204837, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: przegląd literatury i analiza wyników oraz krytyczna rewizja manuksyptu (5%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (60%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

Prof. dr hab. Jolanta Małyszko
specjalista nefrolog
hipertensjolog, transplantolog kliniczny.
choroby wewnętrzne
3365446

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Joanna Raszeja-Wyszomirska

(imię i nazwisko)

OŚWIADCZENIE

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Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (60%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

Prof. dr hab. n. med. Joanna Raszeja-Wyszomirska Klinika Chorób Wewnętrznych I UM w Łodzi

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Maciej Janik

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive Performance in Patients with Alcohol-Associated Liver Disease Undergoing Liver Transplantation. Transpl. Int. 38:12869. doi: 10.3389/ti.2025.12869, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: analiza statystyczna danych (7.5%).

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(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

.....

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Piotr Olejnik

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive Performance in Patients with Alcohol-Associated Liver Disease Undergoing Liver Transplantation. Transpl. Int. 38:12869. doi: 10.3389/ti.2025.12869, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: zbieranie i gromadzenie danych (7.5%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (60%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

Piotr Olejnik

(podpis oświadczającego)

*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Aleksandra Golenia

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive Performance in Patients with Alcohol-Associated Liver Disease Undergoing Liver Transplantation. Transpl. Int. 38:12869. doi: 10.3389/ti.2025.12869, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: koncepcja badania, przegląd literatury (5%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (60%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

(imię i nazwisko kandydata do stopnia)

Aleksandra Golenia

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*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

Warszawa, 19.09.2025

(miejscowość, data)

Jolanta Małyszko

(imię i nazwisko)

OŚWIADCZENIE

Jako współautor pracy pt. Cognitive Performance in Patients with Alcohol-Associated Liver Disease Undergoing Liver Transplantation. Transpl. Int. 38:12869. doi: 10.3389/ti.2025.12869, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: koncepcja badania, nadzór merytoryczny i przegląd literatury (5%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (60%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

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Joanna Raszeja-Wyszomirska

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OŚWIADCZENIE

Jako współautor pracy pt. Cognitive Performance in Patients with Alcohol-Associated Liver Disease Undergoing Liver Transplantation. Transpl. Int. 38:12869. doi: 10.3389/ti.2025.12869, oświadczam, iż mój własny wkład merytoryczny w przygotowanie, przeprowadzenie i opracowanie badań oraz przedstawienie pracy w formie publikacji stanowi: koncepcja badania, przegląd literatury, tworzenie manuskryptu (15%).

Wkład lek. Magdaleny Grusieckiej-Stańczyk w powstawanie publikacji obejmował:

(imię i nazwisko kandydata do stopnia)

badanie pacjentów, zbieranie danych, przegląd literatury, krytyczną analizę uzyskanych wyników oraz przygotowanie manuskryptu (60%).

(merytoryczny opis wkładu kandydata do stopnia w powstanie publikacji) *

Jednocześnie wyrażam zgodę na wykorzystanie w/w pracy jako część rozprawy doktorskiej lek. Magdaleny Grusieckiej-Stańczyk

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*w szczególności udziału w przygotowaniu koncepcji, metodyki, wykonaniu badań, interpretacji wyników

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ZAŁĄCZNIK: NARZĘDZIE DIAGNOSTYCZNE ACE-III (PEŁNA WERSJA)

ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III
Wersja A (2013) – copyright prof. John Hodges
Wersja polska - wstępna

Opracowanie wersji polskiej: M. Senderecka, J. Zabawa, M. Greń, A. Konkel, M. Kuklińska, K. Kluj-Kozłowska, E. Paprot, R. Sikorski, A. Barczak, E. Sitek
Konsultacja językowa i merytoryczna: prof. Thomas Bak
Pytania i uwagi prosimy kierować pod adres: emsitek@gmail.com

Imię i nazwisko osoby badanej:……....	Matura: tak / nie (zakreśl właściwe)
……...	Ręczność: P / L / LP-przeuczony (zakreśl właściwe)
Data urodzenia: _ _ - _ _ - _ _ _ _	
Wykształcenie: podstawowe, zawodowe, średnie, wyższe	Data przeprowadzenia badania: _ _ - _ _ - _ _ _ _
Liczba lat nauki:……	Miejsce przeprowadzenia badania:……....
Zawód:……....	Imię i nazwisko osoby przeprowadzającej badanie:……....

UWAGA

➢ Zadaj pytanie:

Jaki jest dzisiaj dzień tygodnia? _____
Którego dzisiaj mamy? _____
Jaki jest teraz miesiąc? _____
Jaki jest teraz rok? _____
Jaka jest teraz pora roku? _____

Uwaga [Wynik 0-5]: ☐

➢ Zadaj pytanie:

Na którym piętrze/w jakim pomieszczeniu obecnie się znajdujemy? _____
Gdzie się obecnie znajdujemy? (nazwa szpitala/ulicy) _____
W jakim mieście obecnie się znajdujemy? _____
W jakim województwie obecnie się znajdujemy? _____
W jakim kraju obecnie się znajdujemy? _____

Uwaga [Wynik 0-5]: ☐

UWAGA

➢ Powiedz: **„Za chwilę powiem trzy słowa. Proszę je za mną powtórzyć: śliwka, klucz, piłka”**.
Po powtórzeniu słów przez osobę badaną, powiedz: **„Proszę postarać się zapamiętać te słowa, ponieważ zapytam o nie później”**.

➢ Oceń tylko pierwszą próbę (zadanie powtórz maksymalnie 3 razy, jeśli będzie to konieczne).
Odnotuj liczbę prób. _____

Uwaga [Wynik 0-3]: ☐

UWAGA

➢ Poproś osobę badaną: „**Proszę od 100 odjąć 7, a następnie od tego, co wyjdzie znów odjąć 7 i tak dalej, aż powiem stop”**.

➢ Jeśli osoba badana pomyli się, nie powinno się jej przerywać. Należy pozwolić jej kontynuować odejmowanie, jednocześnie sprawdzając poprawność kolejnych odpowiedzi (np. 93, 84, 77, 70, 63 – wynik 4).
Zadanie należy przerwać po pięciu wykonanych działaniach (93, 86, 79, 72, 65): ____ ____ ____ ____ ____

Uwaga [Wynik 0-5]: ☐

PAMIĘĆ

➢ Zadaj pytanie: **„Jakie 3 słowa miał(a) Pan(i) przed chwilą powtórzyć i zapamiętać?”**. _____ _____ _____

Pamięć [Wynik 0-3]: ☐

FLUENCJA

➢ Litery
Powiedz: **„Za chwilę wypowiem pewną literę alfabetu. Chciałbym(abym), aby wymienił(a) Pan(i), jak najwięcej słów rozpoczynających się od tej litery, nie mogą to być jednak imiona, nazwiska lub inne nazwy własne. Na przykład, jeśli wypowiem literę 'S', może Pan(i) podać takie słowa, jak „sen, sok, sowa" lub do nich zbliżone. Nie może jednak Pan(i) wymienić słów pisanych wielką literą, takich jak Sylwia czy Słowacja. Czy rozumie Pan(i) zasady tego zadania? Czy jest Pan(i) gotowy(a)? Ma Pan(i) na to jedną minutę. Proszę wymienić jak najwięcej słów, które zaczynają się od litery 'K'"**.

				≥18	**7**
				14-17	**6**
				11-13	**5**
				8-10	**4**
				6-7	**3**
				4-5	**2**
				2-3	**1**
				0-1	**0**
				Wszystkie	**Poprawne**

Fluencja [Wynik 0-7]:

➢ Zwierzęta
Powiedz: **„Teraz proszę wymienić jak najwięcej nazw zwierząt. Litera, od której się zaczynają, nie ma znaczenia"**.

				≥18	**7**
				14-17	**6**
				11-13	**5**
				8-10	**4**
				6-7	**3**
				4-5	**2**
				2-3	**1**
				0-1	**0**
				Wszystkie	**Poprawne**

Fluencja [Wynik 0-7]:

PAMIĘĆ

➢ Powiedz: **„Za chwilę przeczytam imię, nazwisko oraz adres zamieszkania pewnej osoby. Proszę powtórzyć odczytane przeze mnie imię, nazwisko oraz adres. Aby mógł/mogła je Pan(i) dobrze zapamiętać, odczytam je 3 razy. Po pewnym czasie, w dalszej części badania, zapytam Pana(ią) ponownie o te dane".**

➢ Oceń tylko trzecią próbę.

	Próba I	Próba II	Próba III
Andrzej Lisiecki	_____ _____	_____ _____	_____ _____
Al. Kolejowa 27	_____ _____ __	_____ _____ __	_____ _____ __
Sanok	_____	_____	_____
woj. podkarpackie	_____	_____	_____

Pamięć [Wynik 0-7]:

PAMIĘĆ

➢ Poproś osobę badaną: **„Proszę odpowiedzieć na następujące pytania"**.

Jak nazywa się obecny premier Polski? _____

Jak nazywał się papież-Polak? _____

Jak nazywa się obecny prezydent Stanów Zjednoczonych? _____

A. Jak nazywał się prezydent Stanów Zjednoczonych, który zginął w zamachu w latach 60-tych?
B. Jak nazywa się pierwszy przewodniczący związku zawodowego „Solidarność"?
_____
Przyznaj 1 punkt, jeśli odpowiedź na pytanie A lub B jest prawidłowa. Zadaj oba pytania i zanotuj, na które z nich pacjent odpowiedział prawidłowo.

Pamięć [Wynik 0-4]:

JĘZYK

➢ Połóż ołówek i kartkę przed osobą badaną. W ramach próbnego testu, poproś ją: **„Proszę podnieść ołówek, a następnie kartkę”**. Jeśli osoba badana nie wykona polecenia poprawnie, przyznaj 0 punktów i przejdź do kolejnego zadania.

➢ Jeśli osoba badana poprawnie wykona test próbny, przedstaw jej następujące trzy polecenia:
- Poproś osobę badaną: **„Proszę położyć ołówek pod kartką”**.
- Poproś osobę badaną: **„Zamiast kartki proszę wziąć do ręki ołówek”**.
- Poproś osobę badaną: **„Proszę podać mi ołówek po dotknięciu kartki”**.

Uwaga: Połóż ołówek i kartkę przed osobą badaną, zanim wypowiesz każde z poleceń.

Język [Wynik 0-3]:

JĘZYK

➢ Poproś osobę badaną, aby napisała dwa pełne zdania (lub więcej) o swoich ostatnich wakacjach/świętach Bożego Narodzenia/ostatnim weekendzie. Zdania nie powinny zawierać skrótów. Zegnij kartkę tak, aby osoba badana nie widziała kolejnych zadań.

➢ Przyznaj 1 punkt, jeśli osoba badana napisze dwa pełne zdania (lub więcej) na jeden temat; przyznaj kolejny punkt, jeśli zdania będą poprawne pod względem gramatycznym i ortograficznym.

Język [Wynik 0-2]:

JĘZYK

➢ Poproś osobę badaną, aby powtórzyła: **„dżdżownica”**, **„artyleria”**, **„nieprawdopodobny”**, **„szczodrobliwy”**.
Przyznaj 2 punkty, jeśli wszystkie powtórzenia będą poprawne; 1 punkt, jeśli 3 powtórzenia będą poprawne; 0 punktów, jeśli liczba poprawnych powtórzeń będzie równa lub mniejsza od 2.

Język [Wynik 0-2]:

JĘZYK

➢ Poproś osobę badaną, aby powtórzyła: **„Nie wszystko złoto, co się świeci”**.

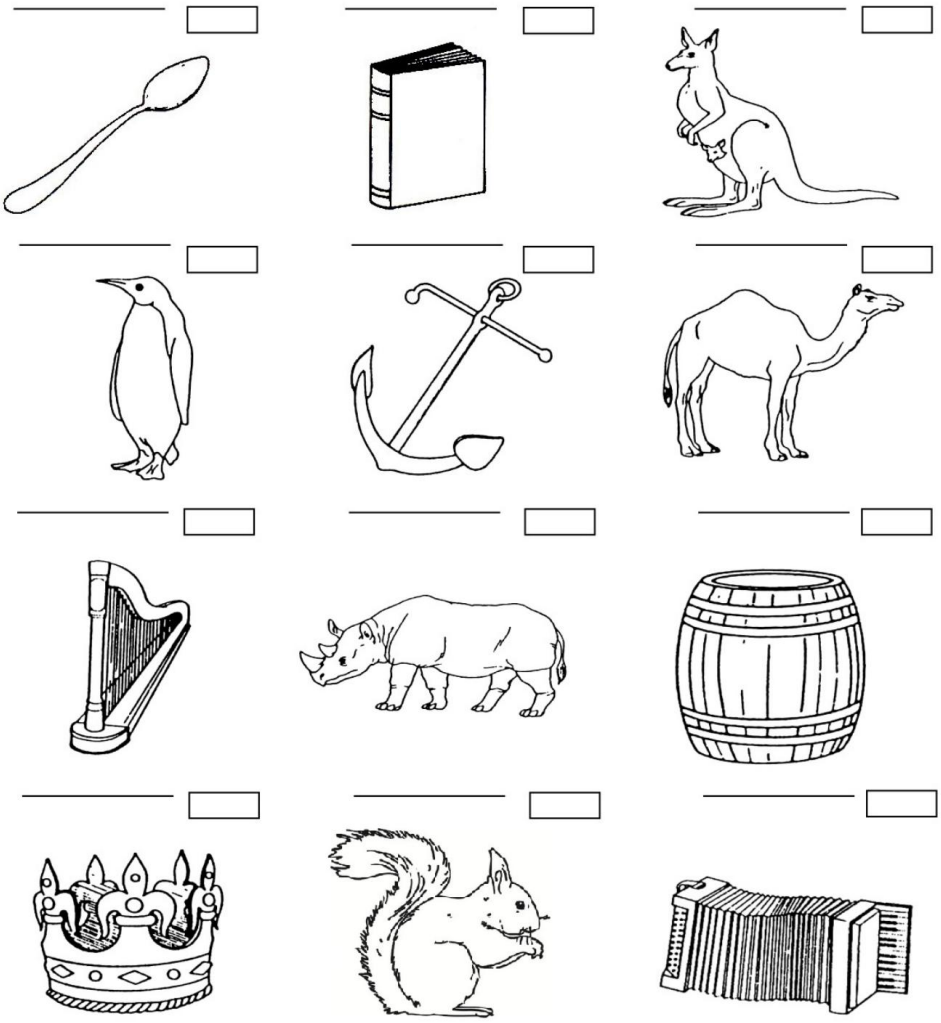
Język [Wynik 0-1]:

➢ Poproś osobę badana, aby powtórzyła: **„Gdzie kucharek sześć, tam nie ma co jeść”**.

Język [Wynik 0-1]:

JĘZYK

➢ Poproś osobę badaną, aby nazwała poniższe obrazki.



Język [Wynik 0-12]:

JĘZYK

➢ Odwołując się do powyższych obrazków, poproś osobę badaną:

- **„Proszę wskazać to, co wiąże się z królestwem”**. _____
- **„Proszę wskazać to, co żyje na Antarktydzie”**. _____
- **„Proszę wskazać to, co jest gryzoniem”**. _____
- **„Proszę wskazać to, co wiąże się z żeglugą”**. _____

Język [Wynik 0-4]:

JĘZYK

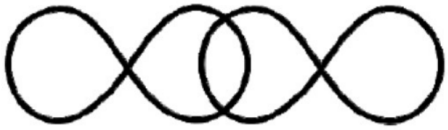
➢ Poproś osobę badaną, aby przeczytała poniższe wyrazy (przyznaj 1 punkt, jeśli wszystkie odczyta poprawnie).

szczur
przód
żubr
ściek
źdźbło

Język [Wynik 0-1]:

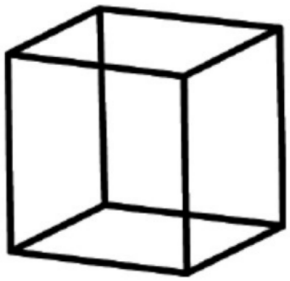
ZDOLNOŚCI WZROKOWO-PRZESTRZENNE

➢ Wstęga Möbiusa: Poproś osobę badaną o przerysowanie obrazka. Zegnij kartkę tak, aby osoba badana nie widziała kolejnych zadań.



Zdolności wzrokowo-przestrzenne [Wynik 0-1]:

➢ Sześcian: Poproś osobę badaną o przerysowanie obrazka (zasady przyznawania punktów opisano w instrukcji). Zegnij kartkę tak, aby osoba badana nie widziała kolejnych zadań.



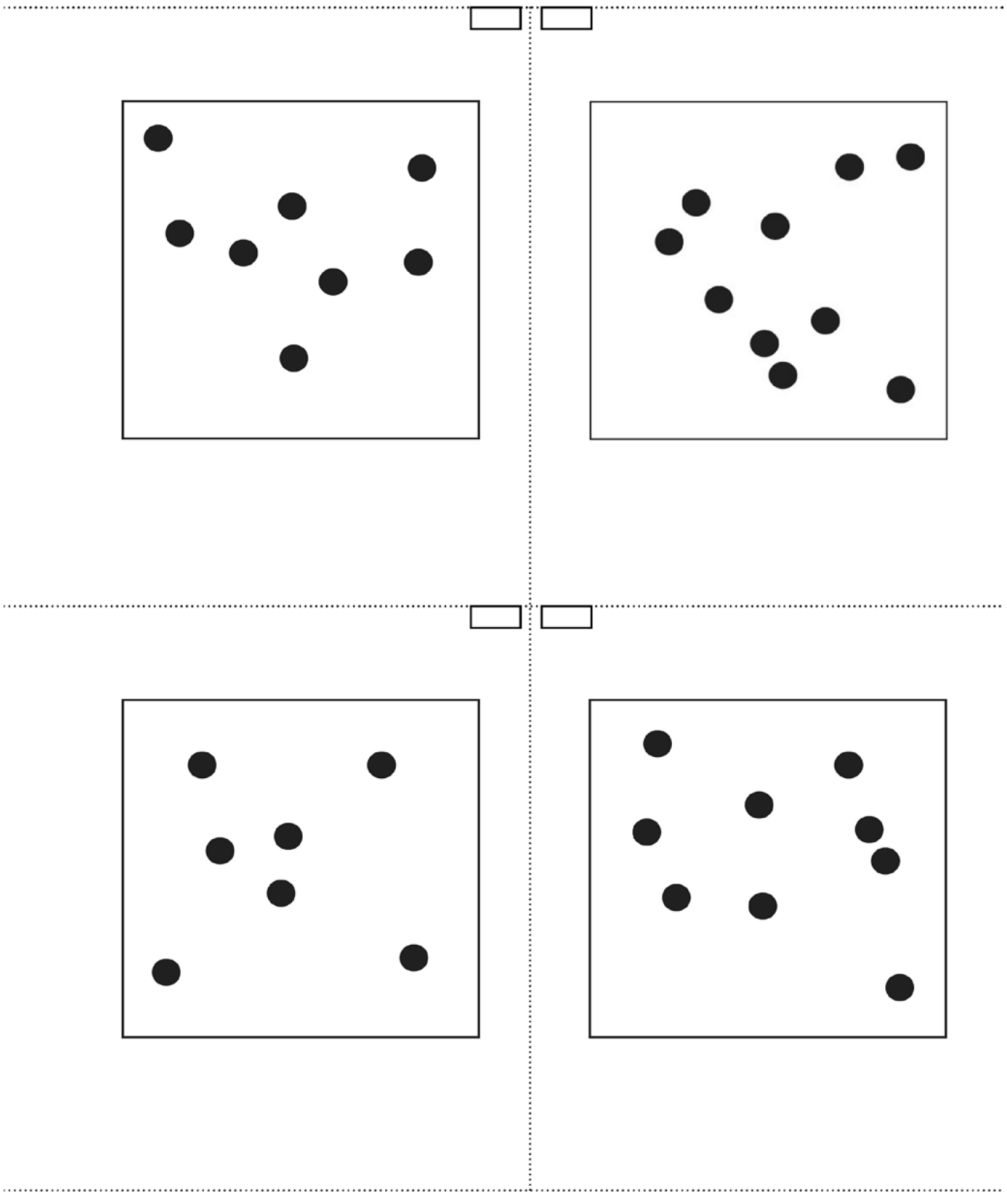
Zdolności wzrokowo-przestrzenne [Wynik 0-2]:

➢ Zegar: Poproś osobę badaną o narysowanie tarczy zegara z liczbami oznaczającymi godziny i wskazówkami nastawionymi na dziesięć po piątej (zasady przyznawania punktów opisano w instrukcji: tarcza=1, liczby=2, wskazówki=2, o ile wymienione elementy zostały przedstawione poprawnie). Zegnij kartkę tak, aby osoba badana nie widziała instrukcji do tego zadania.

Zdolności wzrokowo-przestrzenne [Wynik 0-5]:

ZDOLNOŚCI WZROKOWO-PRZESTRZENNE

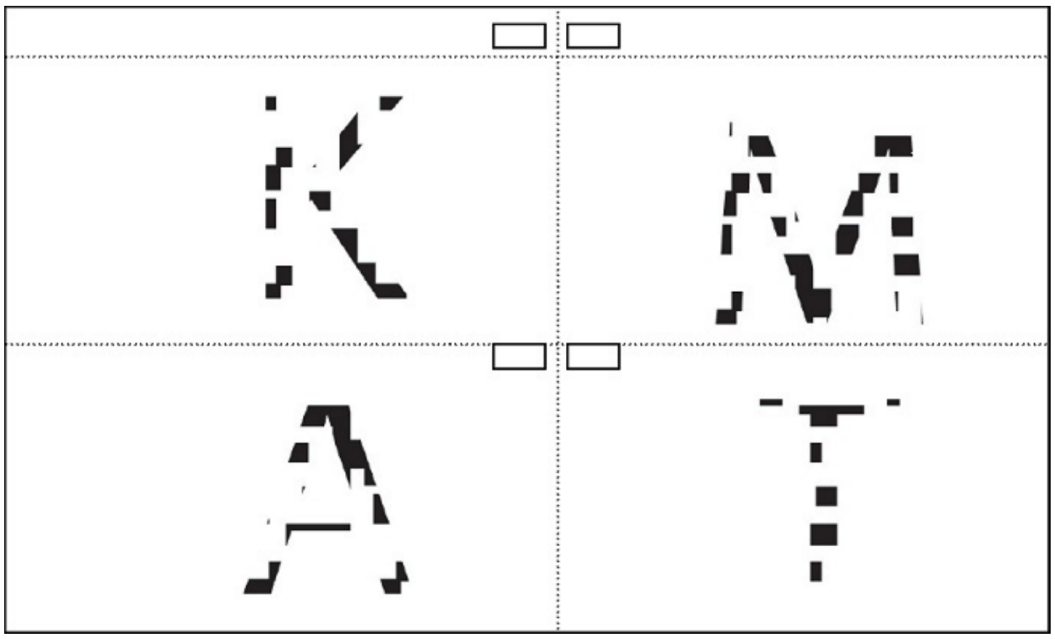
➢ Poproś osobę badaną o policzenie kropek bez wskazywania ich palcem.



Zdolności wzrokowo-przestrzenne [Wynik 0-4]:

ZDOLNOŚCI WZROKOWO-PRZESTRZENNE

➢ Poproś osobę badaną o nazwanie liter. Zegnij kartkę tak, aby osoba badana widząc litery nie widziała adresu.



Zdolności wzrokowo-przestrzenne [Wynik 0-4]:	

PAMIĘĆ

➢ Poproś osobę badaną: **„Proszę spróbować przypomnieć sobie imię, nazwisko oraz adres, które powtarzaliśmy na początku badania”**.

Andrzej Lisiecki	_____ _____
Al. Kolejowa 27	_____ _____ _____
Sanok	_____
woj. podkarpackie	_____

Pamięć [Wynik 0-7]:	

PAMIĘĆ

➢ Test powinien zostać przeprowadzony, jeśli osoba badana nie przypomni sobie któregoś z elementów adresu. Jeśli osoba badana poprawnie odtworzy z pamięci wszystkie dane, należy przyznać jej 5 punktów i zakończyć badanie. Jeśli osoba badana przypomni sobie jedynie część danych, należy zaznaczyć w kolumnie „przypominanie” te, które potrafi poprawnie wymienić. W przypadku pozostałych składników adresu, należy poprosić osobę badaną o dokonanie wyboru właściwej odpowiedzi spośród trzech podanych opcji, np. **„Spróbuję Panu(i) podpowiedzieć, czy imię i nazwisko osoby to X, Y czy Z?”**. Za każdy poprawnie rozpoznany element adresu należy przyznać osobie badanej 1 punkt, a następnie wszystkie uzyskane w ten sposób punkty zsumować z tymi, które uzyskała w teście przypominania.

Paweł Lisiecki		**Andrzej Lisiecki**		**Andrzej Lemański**		przypominanie
Plac Kolejowy		**Al. Dworcowa**		**Al. Kolejowa**		przypominanie
72		**27**		**23**		przypominanie
Łańcut		**Sanok**		**Mielec**		przypominanie
woj. podkarpackie		**woj. małopolskie**		**woj. lubelskie**		przypominanie

Pamięć [Wynik 0-5]:	

WYNIKI	
Uwaga	**/18**
Pamięć	**/26**
Fluencja	**/14**
Język	**/26**
Zdolności wzrokowo-przestrzenne	**/16**
Wynik ogólny ACE-III	**/100**