Predicting Cognitive Impairment in Patients with Chronic Traumatic Encephalopathy: A Single-Center Prospective Cohort Study

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Article

Predicting Cognitive Impairment in Patients with Chronic Traumatic Encephalopathy: A Single-Center Prospective Cohort Study

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Abstract: Chronic traumatic encephalopathy (CTE) is a neurodegenerative condition caused by repeated traumatic brain injuries (TBIs) leading to cognitive, behavioral, and motor dysfunctions. This study examined the relationship between cognitive impairment and clinical syndromes among 145 CTE patients aged 18 to 75 years who underwent inpatient treatment at the Ternopil Regional Clinical Psychoneurological Hospital between 2021 and 2022. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA), with results classified into four categories: normal, mild impairment, moderate impairment, and dementia. Statistical analysis revealed significant associations between cognitive impairment and specific neuroimaging changes, including ventricular dilatation. Clinical syndromes, such as cognitive disorder syndrome, also showed significant associations with cognitive impairment ($p < 0.001$). Using logistic regression, we developed a predictive model to estimate the probability of cognitive impairment based on various clinical features, including memory loss, attention deficits, and sleep disturbances. The model demonstrated high accuracy, with a receiver operating characteristic (ROC) curve showing a sensitivity of 91.0% and a specificity of 92.5%, yielding an area under the curve (AUC) of 0.964 (95% CI: 0.934 - 0.994). These findings suggest that specific neuroimaging and clinical features can predict cognitive impairment in CTE patients.

Keywords: chronic traumatic encephalopathy; traumatic brain injury; cognitive impairment; logistic regression

1. Introduction

Chronic traumatic encephalopathy (CTE) is a unique neurodegenerative tauopathy secondary to recurrent traumatic brain injury (TBI), including concussion, that results in long-term impairments in cognitive, behavioral, affective, and motor functions [1].

In Ukraine, prior to full-scale invasion, the frequency of traumatic injuries to the brain and skull varies across different regions, ranging from 2.3 to 6 cases (averaging 4–4.2) per 1000 people [2]. This increase was primarily attributed to increasing traffic injuries and armed conflict in the east of the country [3]. However, exact statistics on TBIs during the war are currently unavailable. However, according to official data from the Ministry of Health of Ukraine, approximately 200 thousand people were hospitalized with TBI between 2014 and 2019 [4]. Full-scale invasion has led to a critical increase in the number of TBI cases, affecting both military personnel and civilians [5].

It is important to note that neurodegeneration and symptoms of chronic traumatic encephalopathy progress even without further traumatic injuries [6]. While CTE is often associated with contact sports such as American football, boxing, rugby, and wrestling, it is also observed in

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other areas such as equestrian sports (show jumping) and among patients with epilepsy. Furthermore, CTE is found in military veterans and civilians with varying degrees of craniocerebral trauma [7].

The mechanisms underlying the development and progression of CTE are complex and remain poorly understood [8]. Potential mechanisms underlying the neurodegenerative effects of TBI include reductions in cognitive reserve, chronic inflammation, activation of microglia, and a cascade of events involving the release of toxic substances such as cytokines, chemokines, and excitotoxins [9].

Cognitive impairment can result from direct and indirect brain injury, as well as various other factors, such as metabolic disorders, neurodegenerative processes, and exposure to toxins [10]. Additional risk factors for cognitive impairment include advanced age, depression, posttraumatic stress disorder, diabetes, sleep disorders, infections, substance abuse, and polypharmacy [11]. Associations between the clinical characteristics of encephalopathies and cognitive disorders remain unclear.

Therefore, the aim of our study was to analyse the relationships between cognitive functioning, syndromic characteristics, and neuroimaging changes in patients with CTE.

2. Materials and Methods

This study analysed the medical records of 145 patients aged 18 to 75 years with chronic traumatic encephalopathy who received inpatient treatment at the Ternopil Regional Clinical Psychoneurological Hospital from 2021–2022. Diagnosis was performed based on the National Institute of Neurological Medicine (NINDS) criteria, which included: [12]

- **History of repetitive head injuries**: This includes contact sports with a minimum 5-year history or other non-sport-related risks for which specific risk thresholds are yet to be established.

- **Presence of cognitive impairments**: These impairments can involve deficits in episodic memory, executive dysfunction, and/or significant neurobehavioral changes from baseline.

- **Progressive worsening of symptoms**: The symptoms should persist and worsen for at least 1 year without further head trauma.

- **Exclusion of other explanations**: The symptoms should not be fully explained by other conditions, although a comorbid diagnosis of another neurodegenerative disease, neurobehavioral disorder, or substance abuse disorder does not exclude a diagnosis of traumatic encephalopathy syndrome.

- **Additional clinical signs**: These might include a delayed onset of the condition, several years after the last head injury; motor symptoms such as parkinsonism, dysarthria, and ataxia; and psychiatric features such as anxiety, apathy, depression, and paranoia.

Exclusion criteria for patients included the presence of oncopathology, concomitant pathology in the decompensation stage, and the use of medications affecting cognitive and memory functions within at least 4 weeks before inclusion in the study. Patients suspected of having Alzheimer's disease or other degenerative diseases were excluded.

Neuroimaging was performed using multispiral computed tomography (MSCT) (Asteion 4 Toshiba or Toshiba Aquilion TSX-101A/QC, Japan) or magnetic resonance imaging (MRI) (Siemens Magnetom Avantto 1.5 T, with Advanced TIM Technology, Germany).

Cognitive functions were assessed using the Montreal Cognitive Assessment (MoCA), which is a standard method for evaluating cognitive domains. The maximum possible score was 30 points, with a result of 26 points and above considered normal. Scores of 22-25 points indicated mild impairment of cognitive functioning, 19-21 points suggested moderate impairment, and scores below 19 indicated dementia [13].

The statistical analysis of the data was conducted using the computer software jamovi (version 2.2.5). For frequency indicators, the absolute number (n) and percentage (%) are reported. Pearson's χ^2 test was employed to compare frequency characteristics between groups, with a significance level

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of $p < 0.05$ indicating a statistically significant difference between the studied groups. To compare laboratory findings between groups, we used a nonparametric test, the Kruskal–Wallis test, followed by the Dwass–Steel–Critchlow–Fligner (DSCF) post hoc test. The development of a prognostic model for the probability of a binary outcome was carried out using logistic regression. Nagelkerke R^2 was used as a measure of the model performance. ROC analysis was used to assess the diagnostic performance of quantitative variables in predicting a categorical outcome. The optimal cut-off value of the quantitative variable at was estimated using the Youden's J statistic.

3. Results

3.1. Demographic Data

Among the 145 studied patients, the majority were men (131 or 90.3%). The average age was 42 ± 12.1 years (Figure 1). Regarding education levels, most individuals had a middle-level education (79.3%), while a smaller proportion had achieved a higher level of education.

In an effort to understand the connection between education level and cognitive impairment, we analysed the distribution of cognitive impairment across two education groups: "Middle" and "Higher". Within the "Middle" education group, the majority of individuals exhibited mild cognitive impairment, with 16.5% exhibiting normal cognitive function, 80.0% exhibiting mild impairment, and 3.5% exhibiting moderate impairment. For the "Higher" education group, the distribution was slightly different. Here, 16.7% exhibited normal cognitive function, 76.7% had mild impairment, and 6.6% had moderate impairment.

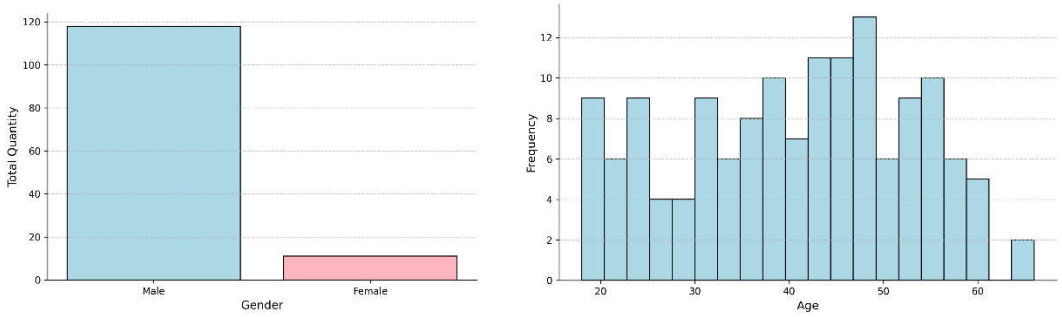

Figure 1. Bar plot of sex (left figure) and age (right figure) distributions in the investigated group. The majority were men (131 of 145 total), with an average age of 42 ± 12.1 years.

The majority of patients were unemployed (112 or 77.2%). The disease duration was as follows: up to 1 year, 23 patients; 1-5 years, 44 patients; 6-10 years, 38 patients; and more than 10 years, 40 patients (Figure 2).

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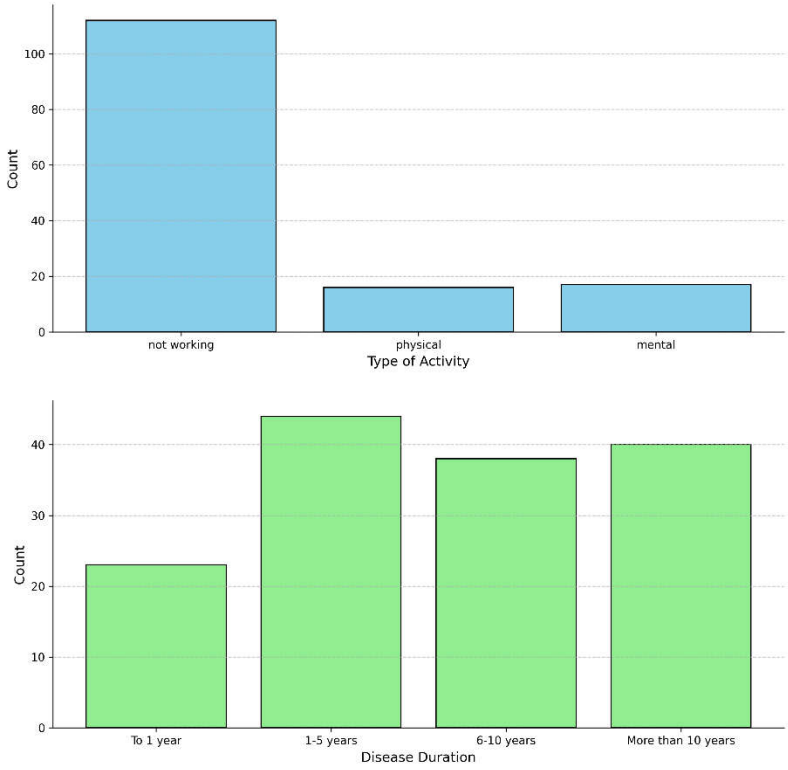

Figure 2. Bar plot of the type of activity (upper plot) and disease duration (lower). The majority of patients were unemployed (112 of 145 total patients).

3.2. Assessment of Cognitive Functions in Patients with Traumatic Encephalopathy Based on Montreal Cognitive Assessment (MoCA) Results Depending on Dominant Clinical Syndromes

Among patients with CTE, cognitive disorder syndrome was present in 88.46% of individuals (Table 1). It is noteworthy that the percentage of patients with cephalic syndrome among those with mild cognitive impairment was 29.29% greater than the number of patients with mild cognitive impairment in whom cephalic syndrome was not present; however, these differences were statistically improbable (Table 1, Figure 3).

Table 1. Evaluation of Cognitive Functions in Patients with Traumatic Encephalopathy Based on the Results of Montreal Cognitive Assessment (MOCA) Analysis Depending on Dominant Clinical Syndromes.

Clinical Syndrome	Norm (%)	Mild (%)	Moderate (%)	χ^2; p
Cephalgic Syndrome	27.14	69.29	3.57	χ^2=2.63; p=0.269
Asthenic Syndrome	27.10	71.03	1.87	χ^2=3.60; p=0.165
Cognitive Disorders Syndrome	8.97	88.46	2.56	χ^2=32.70; p<0.001*
Cerebellar Ataxia Syndrome	24.00	74.00	2.00	χ^2=1.32; p=0.516
Pyramidal	31.34	67.16		χ^2=1.82;

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Insufficiency Syndrome	1.49	p=0.403

* - statistically significant result.

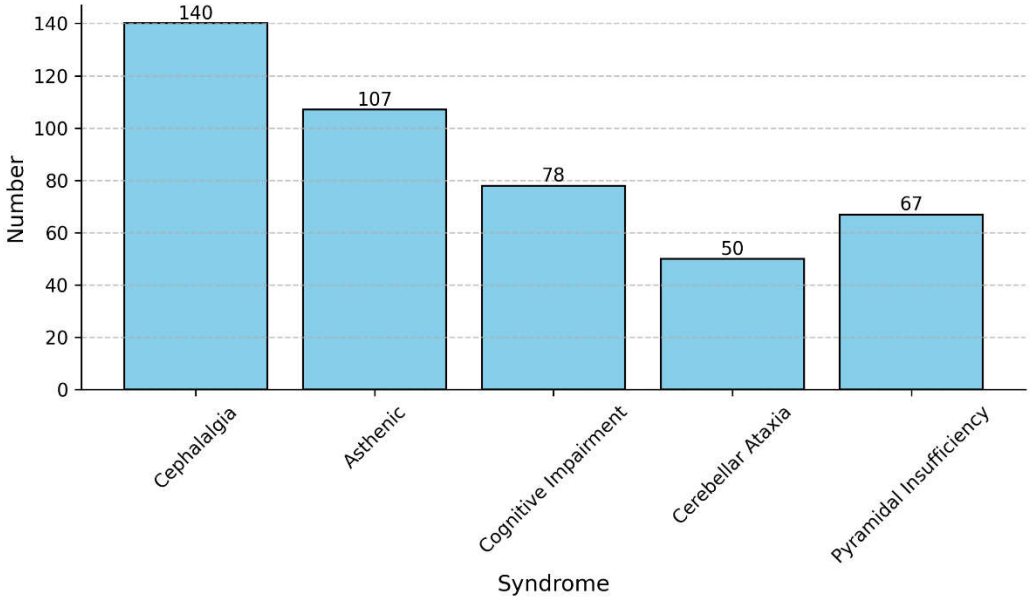

Figure 3. Bar plot of the frequency of different syndromes in patients with chronic traumatic encephalopathy (CTE). Cephalgia was most common in 140 of 145 patients with CTE.

3.3. Evaluation of Cognitive Functions in Patients with Chronic Traumatic Encephalopathy (CTE) Based on Montreal Cognitive Assessment (MoCA) Analysis Depending on Selected Neuroimaging Changes

Among patients with CTE, the percentage of individuals with mild cognitive impairment was nearly the same regardless of the presence of ventricular enlargement. However, among CTE patients diagnosed with ventricular dilatation, the percentage of individuals with moderate cognitive impairment was significantly greater than that among those without ventricular dilatation (10.26% versus 0.94%, respectively) (Table 2, Figure 4).

Table 2. Evaluation of Cognitive Functions in Patients with Traumatic Encephalopathy Based on the Results of Montreal Cognitive Assessment (MOCA) Analysis Depending on Dominant Clinical Syndromes.

Clinical Syndrome	Norm (%)	Mild (%)	Moderate (%)	χ^2; p
Ventricular dilatation	15.38	74.36	10.26	χ^2=10,60; p=0.005*
Enlargement of subarachnoid space	19.64	76.79	3.57	χ^2=3.38; p=0.185
Gliosis	24.64	71.01	4.35	χ^2=1.07; p=0.586
Presence of cysts	23.17	73.17	3.66	χ^2=2.43; p=0.297

* - statistically significant result.

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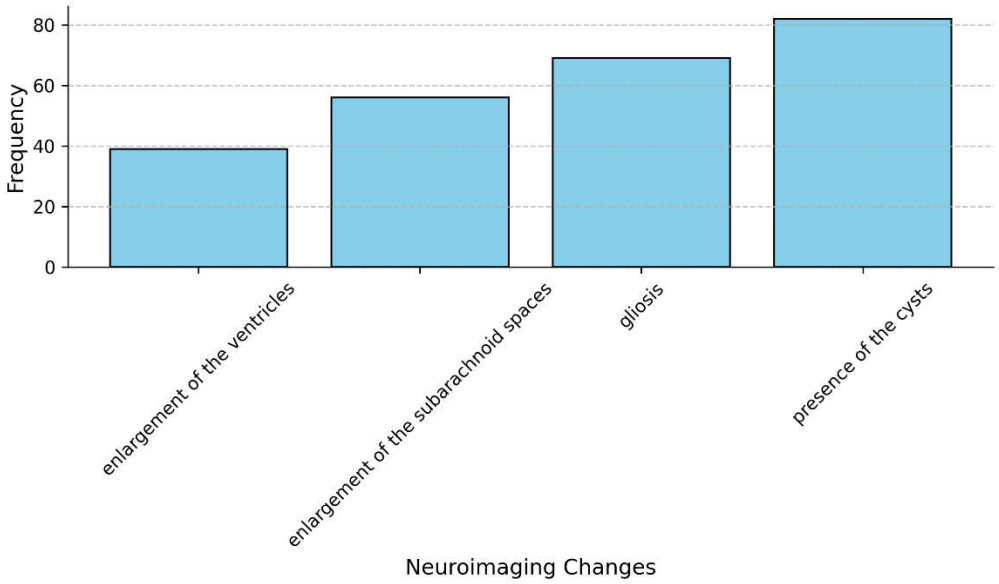

Figure 4. Bar plot of the frequency of neuroimaging findings in patients with chronic traumatic encephalopathy (CTE).

3.4. Evaluation of Cognitive Functions in Patients with Chronic Traumatic Encephalopathy (CTE) Based on Montreal Cognitive Assessment (MoCA) Analysis Depending on Haematological Parameters

To investigate whether blood parameters differ among individuals with varying degrees of cognitive impairment, we applied the Kruskal–Wallis test to a range of hematological indicators across three groups: "mild", "normal", and "moderate". The following results highlight the significant findings and key patterns identified in our analysis. The number of segmented neutrophils significantly differed among the groups ($\chi^2 = 16.5508$, df = 2, $p < 0.001$). Additionally, lymphocyte counts were significantly different across the groups ($\chi^2 = 11.2675$, df = 2, $p = 0.004$), indicating a possible connection between lymphocyte levels and cognitive function. Other blood parameters, including red blood cells (RBCs), haemoglobin (HGB), platelets (PLTs), white blood cells (WBCs), monocytes, the erythrocyte sedimentation rate (ESR), and haematocrit (HCT), did not significantly differ, suggesting that these factors may not vary substantially with the level of cognitive impairment (Table 3).

Table 3. Evaluation of Cognitive Functions in Patients with Traumatic Encephalopathy Based on the Results of Montreal Cognitive Assessment (MOCA) Analysis Depending on Haematological Parameters.

Clinical Syndrome	Norm	Mild	Moderate	p
RBC	5.10 (4.68 - 5.39)	4.95 (4.70 - 5.28)	4.30 (4.20 - 4.67)	0.051
HGB	152 (150 - 154)	148 (141 - 158)	152 (150 - 154)	0.622
PLT	218 (196 - 236)	214 (189 - 254)	231 (190 - 272)	0.944

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WBC	5.92 (5.25 - 7.01)	6.47 (5.10 - 7.60)	5.77 (5.54 - 7.07)	0.598
Segmented Neutrophils	51 (30.0 - 40.0)	60 (22.0 - 35.9)	47 (32.9 - 38.0)	<0.001*
Lymphocytes	36.0 (30.0 - 40.0)	30.00 (22.0 - 35.9)	36.0 (32.9 - 38.0)	0.004*
Monocytes	7.00 (4.00 - 9.00)	7.00 (5.00 - 8.00)	7.10 (2.00 - 7.50)	0.958
Erythrocyte Sedimentation Rate	5.00 (3.00 - 10.0)	5.00 (3.00 - 11.0)	3.00 (2.00 - 7.00)	0.475
Hematocrit	46.5 (43.2 - 48.1)	45.5 (42.7 - 48.0)	46.8 (44.8 - 48.2)	0.706

* - statistically significant result.

3.5. Logistic Regression (Prediction of Probability of Cognitive Impairment)

A predictive model was developed to estimate the probability of cognitive impairment conditioning on angiospasm, venous stasis, vertebrobasilar insufficiency, memory loss (decrease), decreased attention, slow movement, sleep disturbance, hearing loss, general weakness, anxiety, brief disorientation, motor system disorders (paresis), vestibulo-cochlear, SAS enlargement, irritation of brainstem structures, and angiospasm-carotid distribution using binary logistic regression.

The observed association can be described by the following equation:

$P = \frac{1}{1+e^{-z}} \times 100\%$. where P is the probability of "yes". and condition is present (0 for no. 1 for yes) for each predictor. such as angiospasm. venous stasis. etc.; z = -2.623 - 7.162× angiospasm - 2.572× venous stasis - 5.073× vertebrobasilar insufficiency + 4.914× memory loss (decrease) + 5.380× decrease in attention - 4.186× slowness of movement - 2.700× decrease in attention - 6.391× slowness of movement - 1.892× sleep disturbance - 2.954× hearing loss + 5.716× general weakness - 3.043× anxiety + 5.747× brief disorientation + 3.154×motor system disorders (paresis) + 3.049× irritation of brainstem structures + 7.799×angiospasm - carotid distribution (Table 4, Figure 5).

Table 4. Characteristics of the association of predictors with the probability of cognitive impairment.

Predictors	Unadjusted		Adjusted	
	COR; 95% CI	p value	AOR; 95% CI	p value
angiospasm: yes	0.953; 0.494 – 1.839	0.886	0.001; 0.000 – 0.074	0.002*
venous stasis: yes	0.776; 0.398 – 1.510	0.455	0.076; 0.014 – 0.425	0.003*
vertebrobasilar insufficiency: yes	0.382; 0.135 – 1.081	0.070	0.006; 0.000 – 0.085	< 0.001*
memory loss (decrease): yes	19.999; 8.449 – 47.371	< 0.001*	136.210; 17.253 – 1074.918	< 0.001*

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decreasement of attention: yes	11.294; 3.241 – 39.370	< 0.001*	217.109; 14.865 – 3168.457	< 0.001*
slowness of movement: yes	1.757; 0.312 – 9.905	0.523	0.015; 0.001 – 0.317	0.007*
sleep disturbance: yes	0.544; 0.244 – 1.217	0.138	0.067; 0.010 – 0.452	0.005*
hearing loss: yes	0.939; 0.447 – 1.970	0.867	0.002; 0.000 – 0.063	0.001*
general weakness: yes	1.344; 0.698 – 2.586	0.377	0.151; 0.031 – 0.736	0.019*
anxiety: yes	0.841; 0.313 – 2.257	0.730	0.052; 0.004 – 0.678	0.024*
brief disorientation: yes	3.568; 0.389 – 32.720	0.261	303.627; 4.674 – 19732.060	0.007*
motor system disorders (paresis): yes	0.697; 0.311 – 1.562	0.381	0.048; 0.006 – 0.350	0.003*
vestibulo-cochlear: yes	0.993; 0.481 – 2.048	0.984	313.093; 10.528 – 9311.449	0.001*
SAS enlargement: yes	2.280; 1.140 – 4.559	0.020*	23.427; 3.740 – 146.790	0.001*
irritation of brainstem structures: yes	2.237; 0.970 – 5.160	0.059	21.101; 2.770 – 160.774	0.003*
angiospasm - carotid distribution: yes	1.606; 0.811 – 3.184	0.175	2438.894; 20.471 – 290686.312	0.001*

* - statistically significant result.

The resulting regression model is statistically significant ($p < 0.001$). Based on the Nagelkerke R^2. The model explained 78.6% of the observed cognitive impairment variance (Figure 6,7).

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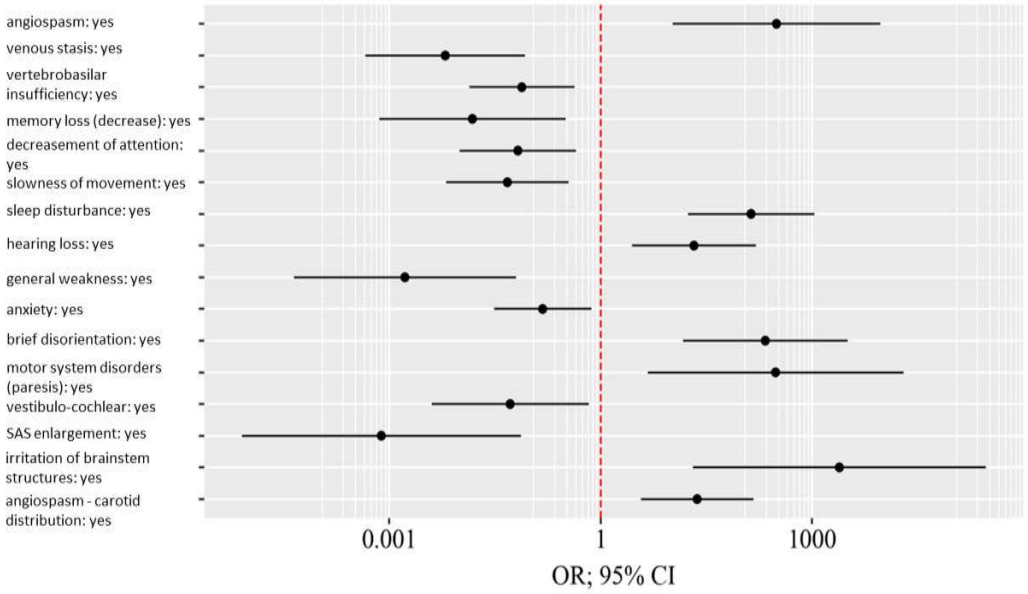

Figure 5. Odds ratio estimates with corresponding 95% CIs for predictors included in the logistic regression model.

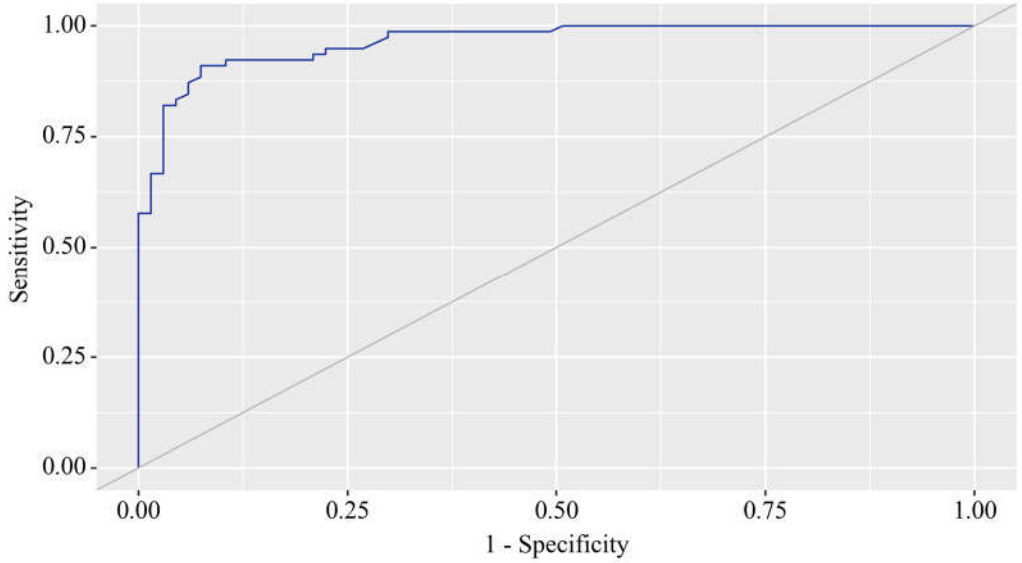

Figure 6. Receiver operating characteristic (ROC) curve for the predictive accuracy of the logistic regression model for CTE-related cognitive impairment. The sensitivity and specificity of the curve were 91.0% and 92.5%, respectively. The area under the ROC curve was 0.964 ± 0.015 (95% CI: 0.934 - 0.994). The resulting model was statistically significant ($p < 0.001$). The diagonal line (gray line) denotes the ROC curve of a random classifier.

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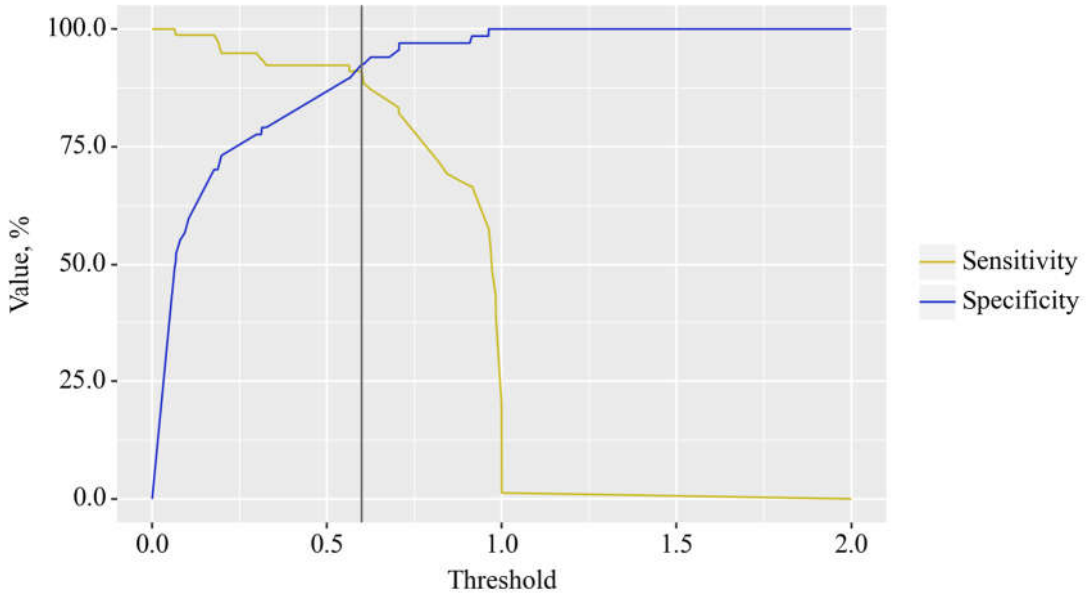

Figure 7. Cut-off Plot for Optimal Threshold Selection in a Logistic Regression Model for Predicting CTE-Related Cognitive Impairment.

4. Discussion

The present study investigated the relationships between neuroimaging changes, clinical syndromes, and cognitive impairment in patients with chronic traumatic encephalopathy (CTE). Using the Montreal Cognitive Assessment (MoCA), we classified the severity of cognitive impairment in 145 patients, revealing that the majority displayed mild to moderate cognitive deficits. Our findings shed light on the underlying mechanisms of cognitive decline in CTE patients and suggest potential markers for early detection and intervention.

The analysis of neuroimaging data highlighted a significant association between ventricular dilatation and moderate cognitive impairment, indicating that neuroanatomical changes may serve as valuable indicators of disease progression [14,15]. This finding aligns with previous research suggesting that structural changes in the brain can reflect the cumulative effects of repeated traumatic brain injuries (TBIs) [16]. However, other neuroimaging features, such as enlargement of the subarachnoid space and the presence of cysts, showed no statistically significant correlation with cognitive impairment.

There has been growing interest in determining whether intracranial arachnoid cysts are responsible for psychological or psychiatric issues. Various disorders have been associated with cysts that impact the temporal and frontal lobes; for a comprehensive analysis, refer to Wester [17]. Only a limited number of studies have systematically investigated the impact of cysts on cognition in a large group of patients before and after surgical decompression. These studies consistently show that temporal cysts can negatively affect various fundamental aspects of cognition. Importantly, they also demonstrated that cognition returns to normal after surgical cyst decompression [18–20]. The process of normalizing cognition may begin as soon as 4 hours after surgery [20]. Tomofumi Nishikawa et al. reported that ventricular enlargement, in combination with a disproportionately enlarged subarachnoid space, plays an essential role in worsening cognitive function in patients with DESH [21].

In terms of clinical syndromes, cognitive disorder syndrome was highly prevalent among patients with CTE, with a notable link to mild to moderate cognitive impairment. This finding suggests that cognitive deficits are an inherent part of the syndrome and underscores the importance of monitoring these symptoms in individuals with a history of repeated head trauma [22]. Interestingly, cephalgic syndrome and asthenic syndrome were also common, although their correlation with cognitive impairment was not statistically significant. Additionally, scientists have

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reported that higher education decreases vulnerability to cognitive dysfunction and facilitates recovery following traumatic brain injury (TBI) [23].

Our logistic regression model demonstrated a high level of accuracy in predicting cognitive impairment based on a combination of clinical factors, including memory loss, attention deficits, and slowness of movement. The model's high sensitivity and specificity suggest that it could serve as a useful tool for clinicians in assessing the risk of cognitive decline in CTE patients. However, the variability in the individual contributions of different predictors indicates the complexity of CTE and the multifaceted nature of its symptoms.

Several limitations should be acknowledged. First, the study sample was derived from a single clinical center, which may limit the generalizability of the findings. Additionally, the retrospective nature of the data and the lack of longitudinal follow-up constrain our ability to draw causal inferences. Future studies with larger, more diverse cohorts and longitudinal designs could provide a more comprehensive understanding of the progression of CTE and its relationship to cognitive impairment.

Despite these limitations, our study offers important insights into the neurodegenerative aspects of CTE and identifies potential markers for early detection. The predictive logistic regression model has practical applications for clinical assessment and could inform the development of targeted interventions to mitigate cognitive decline. Ultimately, this study underscores the need for continued research into the underlying mechanisms of CTE and the development of effective strategies to manage and prevent cognitive impairment in patients with a history of repeated TBIs.

Author Contributions: Conceptualization. K.D. and O.K.; software. O.K.; validation. V.O., P.P. and K.D.; formal analysis. O.K.; investigation. K.D.; resources. K.D.; data curation. K.D. and O.K.; writing—original draft preparation. K.D. and P.P.; writing—review and editing. O.O. and V.O.; visualization. P.P.; supervision. K.D. and O.K.; project administration. K.D.; funding acquisition. V.O. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Commission of Bioethical Expertise and Research Ethics of the I. Horbachevsky Ternopil National Medical University. Ministry of Health. Ukraine (report No. 74 dated September 1st. 2023).

Informed Consent Statement: Informed consent was obtained from all the subjects involved in the study. Written informed consent was obtained from the patients to publish this paper.

Data availability statement: The data presented in this study are available upon request from the corresponding author.

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

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