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Diagnostic value and correlation analysis of deregulated oxy-Hb disorder in cognitive impairment in patients with alcohol dependence

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Summary. Aim. To explore the expression of oxygenated hemoglobin (oxy-Hb) in the brain of patients with alcohol dependence. Further, to evaluate the diagnostic value of oxy-Hb in the cognitive impairment of patients with alcohol dependence. **Methods.** Seventy-one alcohol-dependent adults and 70 healthy adults were recruited in the observation and control groups, respectively. The oxy-Hb level and scores of Wisconsin card sorting test, brief visuospatial memory test-revised, digital sequence test, digital span test, and continuous performance test were recorded and compared between the two groups. Further, the sensitivity and specificity of the oxy-Hb level for the diagnosis of cognitive impairment in patients with alcohol dependence were evaluated by drawing an ROC curve. Moreover, the correlation between the oxy-Hb level and cognitive function test scores was analyzed by Pearson's correlation analysis. **Results.** During cognitive activities, the oxy-Hb levels in the observation group were lower than those in the control group ($p<0.001$). The area under the curve (AUC) of oxy-Hb was 0.930, and the sensitivity and specificity were 89.1% and 84.0%, respectively. The scores of responses administered, trials to compete first category, perseverative responses, and the perseverative response errors in executive function in the observation group were higher than those in the control group ($p<0.001$), whereas the correct responses score and categories completed score were lower than those in the control group ($p<0.001$). Similarly, the memory and attention scores of the observation group were lower than those of the control group ($p<0.001$). Moreover, the scores of correct responses, categories completed, brief visuospatial memory test-revised, digital sequence test, digital span test, and continuous performance test were positively correlated with the level of oxy-Hb ($p<0.05$). However, the scores of responses administered, trials to compete first category, and perseverative response errors were negatively correlated with the oxy-Hb level ($p<0.001$). **Conclusions.** The oxy-Hb levels are reduced in patients with alcohol dependence and have high diagnostic accuracy for cognitive impairment in such patients.

Key words. Alcohol-dependent, cognitive impairment, diagnosis, oxy-Hb.

Valore diagnostico e analisi di correlazione del disturbo ossi-Hb deregolato nel deterioramento cognitivo nei pazienti con dipendenza da alcol.

Riassunto. Scopo. Esplorare l'espressione dell'emoglobina ossigenata (ossi-Hb) nel cervello di pazienti con dipendenza da alcol. Inoltre, valutare il valore diagnostico di ossi-Hb nel deterioramento cognitivo dei pazienti con dipendenza da alcol. **Metodi.** Settantuno adulti alcoldipendenti e 70 adulti sani sono stati reclutati rispettivamente nei gruppi di osservazione e di controllo. Il livello di ossi-Hb e i punteggi del test di selezione di carte di Wisconsin, del test di memoria visuospaziale breve rivisto, del test di sequenza digitale, del test di span digitale e del test delle prestazioni continue sono stati registrati e confrontati tra i due gruppi. Inoltre, la sensibilità e la specificità del livello di ossi-Hb per la diagnosi di deterioramento cognitivo nei pazienti con dipendenza da alcol sono state valutate disegnando una curva ROC. La correlazione tra il livello di ossi-Hb e i punteggi dei test delle funzioni cognitive è stata analizzata dall'analisi di correlazione di Pearson. **Risultati.** Durante le attività cognitive, i livelli di ossi-Hb nel gruppo di osservazione erano inferiori a quelli del gruppo di controllo ($p<0,001$). L'area sotto la curva (AUC) dell'ossi-Hb era 0,930 e la sensibilità e la specificità erano rispettivamente dell'89,1% e dell'84%. I punteggi delle risposte somministrate, le prove per competere nella prima categoria, le risposte perseverative e gli errori di risposta perseverativa nella funzione esecutiva nel gruppo di osservazione erano superiori a quelli del gruppo di controllo ($p<0,001$), mentre il punteggio delle risposte corrette e il punteggio delle categorie completate erano inferiori a quelli del gruppo di controllo ($p<0,001$). Allo stesso modo, i punteggi di memoria e attenzione del gruppo di osservazione erano inferiori a quelli del gruppo di controllo ($p<0,001$). Inoltre, i punteggi delle risposte corrette, delle categorie completate, del breve test di memoria visuospaziale rivisto, del test di sequenza digitale, del test di span digitale e del test continuo delle prestazioni sono stati positivamente correlati con il livello di ossi-Hb ($p<0,05$). Tuttavia, i punteggi delle risposte somministrate, le prove per competere nella prima categoria e gli errori di risposta perseverativa erano correlati negativamente con il livello di ossi-Hb ($p<0,001$). **Conclusioni.** I livelli di ossi-Hb sono ridotti nei pazienti con dipendenza da alcol e hanno un'elevata accuratezza diagnostica per il deterioramento cognitivo in tali pazienti.

Parole chiave. Deterioramento cognitivo, diagnosi, dipendenza da alcol, ossi-Hb.

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Introduction

In the current social scenario, most individuals do not have a correct understanding of alcohol consumption, which results in alcohol abuse and eventually leads to alcohol dependence. Alcohol dependence is a physiological and psychological state induced by repeated alcohol consumption, manifested by a strong craving for alcohol and forced experience of frequent alcohol consumption[1,2]. Patients with alcohol dependence find it challenging to effectively control the occurrence, beginning, end, and dosage of alcohol consumption behavior[3]. After complete or partial abstinence, alcohol withdrawal symptoms, such as tremors, transient hallucination, seizures, and delirium, often appear, and these symptoms rapidly disappear after recover from alcohol consumption[4]. According to a study published in The Lancet Medical Journal, alcohol consumption has increased by 10% from 1990 to 2017, and it is considered that if this trend continues, alcohol consumption will increase by 17% over the next 10 years[5]. Alcoholism can seriously endanger human health and public safety. With the increase in alcohol production and consumption annually, public health problems caused by alcohol abuse are becoming increasingly prominent.

Alcohol can induce damage to the central nervous system, leading to changes in the brain function and structure[6]. Studies have reported that cognitive impairment in patients with alcohol dependence is closely related to white matter atrophy, which affects vision, space, memory, attention, and some other functions, such as blood flow[7]. Pandey et al. reported that executive dysfunction in patients with alcohol dependence was associated with prefrontal lobe damage, whereas memory dysfunction was associated with the hippocampal volume[8]. Findings from previous reports have suggested that most patients with alcohol dependence have different degrees of cerebral hypoperfusion, including that in the cerebral cortex and subcutaneous structural regions, but most researchers believe that the prefrontal cortex is the core region[9]. Oxygenated hemoglobin (oxy-Hb) is a substance produced by the reversible combination of hemoglobin and oxygen molecules, which helps transport oxygen[10]. The blood-oxygen level has been shown to rapidly rise in the human brain engaged in cognitive activities through the action of the neural-vascular matching mechanism, which significantly increases the concentration of oxy-Hb in the cognitive activity area of the brain[11]. Moreover, a study that included patients with schizophrenia showed that the concentration of oxy-Hb in the prefrontal lobe was significantly reduced during cognitive activity when compared to healthy individuals [12].

In the past, findings from several studies have revealed the influence of oxy-Hb levels on the cognitive impairment in patients with alcohol dependence. The aim of this present study was to evaluate the diagnostic value of oxy-Hb in the cognitive impairment of patients with alcohol dependence by measuring the level of oxy-Hb in the prefrontal lobe of patients, thus providing insights into clinical interventions for such patients.

Materials and methods

Study population

Seventy-one male patients with alcohol dependence hospitalized in Hengshui Seventh People's Hospital were selected for the observation group. The inclusion criteria for patients with alcohol dependence were as follows: 1) the diagnosis of the patients should conform to the diagnostic criteria of alcohol dependence in the International Classification of Diseases-10; 2) males age from 30 to 60 years; 3) patients with normal intelligence; 4) patients who stopped drinking alcohol at least 14 days prior to the test and also stopped using alternative sedatives. The exclusion criteria were as follows: 1) patients with organic mental disorders; 2) patients with a history of central nervous system disease, such as stroke, epilepsy, and tumor; 3) patients with a history of serious chronic diseases, such as hypertension and diabetes. Additionally, 70 healthy adult male patients were selected during the same period for the control group. The study was approved by the Ethics Committee of Hengshui Seventh People's Hospital, and all the members who participated in the study had signed the informed consent form after being fully informed.

Collection of sample and measurement of oxy-Hb

In this study, the oxy-Hb content was determined using the ETG-4000 type quantitative imaging device of brain function developed and manufactured by Hitachi. This quantitative imaging device system has 17 optical signal transmitters that emit infrared light of 695 nm and 830 nm and measure the cognitive activities in the subjects' brains during the stimulus tasks to measure the oxy-Hb levels. The device captures infrared signals through a detector in which the sensor is attached to a soft and flexible cloth cover, and the cloth cover is fixed on the forehead of the subject to examine the frontal lobe of the brain. The oxy-Hb level was measured using this imaging device, and the data were analyzed using the VerL.61e system analysis software attached to the test instrument.

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Cognitive function assessment

Two technicians specializing in psychological assessment evaluated the patients with alcohol dependence who stopped taking antipsychotic medications. Subjects were required to complete the Wisconsin card sorting test (WCST), brief visuospatial memory test-revised (BVMT-R), digital sequence test, digital span test, and continuous performance test (CPT).

The subjects completed the WCST after selecting six correct categories. During the test, subjects were unaware of the category principle, and the system automatically informed the subjects of the results. The responses administered, correct responses, categories completed, trials to compete first category, perseverative responses, and perseverative response errors of subjects were recorded. BVMT-R primarily measured the memory ability of subjects. The total score was the sum of the scores of three tests. The higher the total score, the stronger the memory ability of the subjects. Similarly, the digital sequence test measured the operating memory ability of subjects. The test took approximately 5 min to complete, with 1 and 0 points awarded for correct and wrong responses, respectively. A higher total score corresponded to a higher operational memory ability. Meanwhile, the digital span test measured the attention and short-term memory of subjects. A higher score indicated a higher level of attention. Further, CPT was used to examine the sustained attention level of subjects, which is the"maintenance factor" of attention and is related to the level of arousal. Reaction time, reaction time change index, number of mistakes and omissions of subjects were recorded, and a subject with a higher score was considered to have a higher level of attention.

Data analysis

SPSS 22.0 was used for data processing. The quantitative data followed the normal distribution and were represented by mean±standard deviation (x±SD). The independent sample *t*-test was used for comparison between two groups. Moreover, the results of the correlation study were analyzed using the Pearson correlation coefficient method. Further, the receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of oxy-Hb in alcohol-dependent cognitive dysfunction. $P<0.05$ indicated that the difference was statistically significant.

Results

Oxy-Hb content in patients with alcohol dependence

A total of 141 subjects were tested, which included 70 healthy subjects and 71 patients with alcohol dependence. No statistically significant differences were observed between the two groups in terms of age, BMI, smoking history, and education level; hence, the groups were comparable (table 1), ($p>0.05$). The results revealed a significant declining trend in the levels of oxy-Hb in the brains of patients with alcohol dependence as compared to that in healthy individuals (Figure 1), ($p<0.001$).

Comparison of cognitive function scores between the observation and control groups

As shown in table 2, the scores of responses administered, trials to compete first category, perseverative responses, and perseverative response errors

Table 1. Clinical data of the study population.

Variables	All subjects (n=141)		*P* value
	Healthy individuals (n=70)	Alcohol dependence (n=71)	
Age	47.33±7.77	49.14±8.14	0.177
BMI	23.51±2.84	23.54±2.97	0.959
Smoking status (n)			**0.052**
Yes	28	40	
No	42	31	
Education Level (n)			**0.271**
Junior high and below	30	37	
Junior high school above	40	34	

Legend: BMI= body mass index.
Data are expressed as n or mean ± standard deviation.

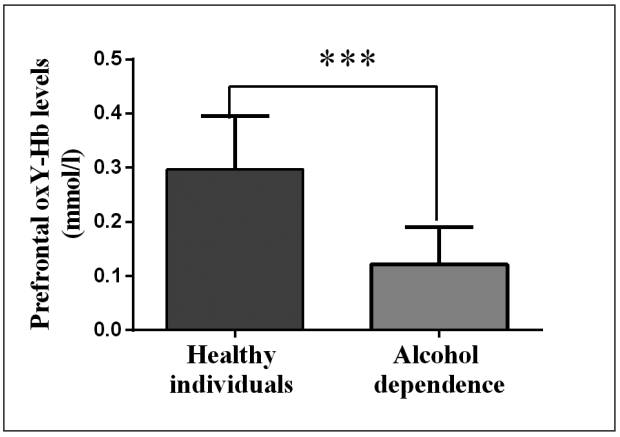

Figure 1. The concentration of oxygenated hemoglobin (oxy-Hb) in the frontal lobe of patients with alcohol dependence decreased compared to that in healthy controls.
***$P < 0.001$.

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Table 2. Comparison of cognitive function test scores between groups.

Variables	All subjects (N=141)		*P* value
	Healthy individuals (n=70)	Alcohol dependence (n=71)	
Executive function			
Response administered	106.73±8.91	139.91±17.43	<0.001
Correct responses	71.47±6.19	46.31±6.54	<0.001
Categories completed	4.81±0.80	1.58±0.62	<0.001
Trials to compete first category	24.42±5.68	58.28±10.65	<0.001
Perseverative responses	26.24±5.09	38.22±8.35	<0.001
Perseverative responses errors	20.79±6.84	34.79±6.18	<0.001
Memory function			
Brief visuospatial memory test-revised	29.00±1.69	18.30±2.97	<0.001
Digital sequence test	27.40±2.22	18.31±3.00	<0.001
Attention function			
Digital span test	20.89±2.22	14.89±1.78	<0.001
Continuous performance test	3.00±0.80	1.75±0.68	<0.001

were higher, whereas the scores of correct responses and categories completed were lower in the observation group as compared to that in control group ($p<0.001$). Moreover, the scores of memory function (BVMT-R, digital sequence test) and attention function (digital span test, CPT) were significantly lower in the observation group than in the control group ($p<0.001$).

Correlation between the oxy-Hb level and cognitive function scores in patients with alcohol dependence

Pearson correlation analysis has shown that the scores of correct responses, categories completed, BVMT-R, digital sequence test, digital span test, and CPT were positively correlated with the levels of oxy-Hb (table 3), ($p<0.05$). However, the scores of administered, trials to compete first category, and perseverative response errors were negatively correlated with the oxy-Hb levels ($p<0.001$). Besides, no correlation was observed between the score of perseverative response and oxy-Hb level ($p=0.108$).

Table 3. Correlation between relative concentration of Oxy-Hb and various indicators.

Variables	Alcohol dependence group (n=71)	
	r	p
Executive function		
Response administered	-0.749	<0.001
Correct responses	0.401	0.001
Categories completed	0.293	0.013
Trials to compete first category	-0.827	<0.001
Perseverative responses	-0.193	0.108
Perseverative response errors	-0.693	<0.001
Memory function		
Brief visuospatial memory test-revised	0.601	<0.001
Digital sequence test	0.333	0.005
Attention function		
Digital span test	0.577	<0.001
Continuous performance test	0.494	<0.001

Diagnostic value of oxy-Hb in cognitive impairment in patients with alcohol dependence

Patients in the observation group received MMSE and MoCA tests and were categorized into cognitive impairment and non-cognitive impairment groups according to the results (results shown in table 4). As illustrated in figure 2A, the oxy-Hb levels in patients with cognitive impairment were lower than those in the non-cognitive impairment group ($p<0.001$). Subsequently, the oxy-Hb in the observation group was analyzed by ROC analysis. As shown in figure 2B, the area under ROC curve of the oxy-Hb level in the observation group was 0.930 at the cut-off value of 0.135, and 95% CI was 0.874-0.987. The sensitivity and specificity of oxy-Hb in the diagnosis of alcohol-dependent cognitive dysfunction were 89.1% and 84.0% respectively.

Discussion and conclusions

Cognition is the process in which the individual's sensory organs process external information input and convert it into an individual's internal psychological activities[13]. These activities mainly include

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Table 4. Comparison of MMSE and MoCA scores between two groups.

Variables	Alcohol-dependent patients (n = 71)		P value
	Poor cognitive function (n = 22)	Good cognitive function (n = 49)	
MMSE score	21.36 ± 1.62	25.75 ± 1.60	< 0.001
MoCA score	20.45 ± 1.92	27.55 ± 1.19	< 0.001

Legend: MMSE= Mini-Mental State Examination; MoCA= Montreal Cognitive Assessment.
Data are expressed as n or mean ± standard deviation.

perception, memory, attention, thinking, language, and orientation. The factors that may directly or indirectly cause structural and functional damage to the cerebral cortex can cause cognitive dysfunction in individuals through different mechanisms that include chronic brain tissue injury, chronic systemic diseases, mental and psychological abnormalities, and other humanistic factors[14,15]. Cognitive dysfunction adversely affects different aspects of an individual's regular life, including study, work, and social relationships. The mechanism underlying cognitive impairment in patients with alcohol dependence has not yet been clarified, but it is considered to be related to the central nervous system damage caused by the neurotoxic effect of alcohol. In humans, the prefrontal cortex is primarily involved in advanced cognitive functions, such as perception, memory, execution, decision-making, attention, and reasoning[16]. By measuring the change in the oxy-Hb concentration in the prefrontal cortex during cognitive activities, we can preliminarily determine whether the cerebral hemodynamics of subjects is normal or whether there is the possibility of damage.

Alcohol is an inhibitor of the central nervous system and exerts a direct toxic effect on the nervous system, which can alter brain function and structure[17,18]. Studies have shown that patients with alcohol dependence show varying degrees of decreased cerebral blood perfusion and cerebral blood flow in the prefrontal lobe[19]. These pathological factors may cause diffuse cerebral blood supply insufficiency, severe brain hypoxia, or even brain atrophy, which may directly induce cognitive dysfunction in patients with alcohol dependence[20]. During the cognitive activity of the brain, oxygen consumption and blood perfusion in the brain tissue increase, which upregulates the concentration of oxy-Hb in the active area of the brain tissue[21]. In this study, the oxy-Hb concentration in the prefrontal lobe of patients with alcohol dependence and healthy controls during cognitive activities was measured using a brain function imaging in-

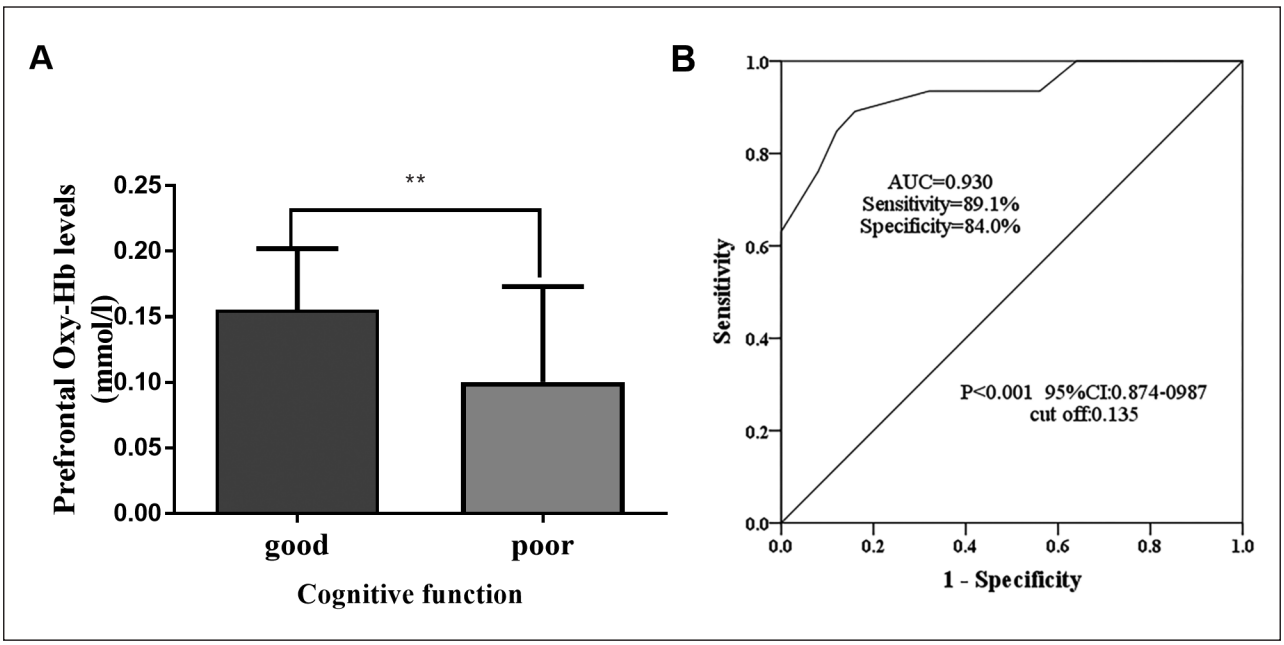

Figure 2. (A) The concentration of oxy-Hb in in patients with poor cognitive function was lower than that in individuals with good cognitive function group; (B) Receiver operating characteristic (ROC) curve analysis. The area under the curve of oxy-Hb was 0.926, and the sensitivity and specificity were 88.7% and 82.9%, respectively.
**$P < 0.001$.

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strument. The results showed that the concentration of oxy-Hb in patients with alcohol dependence was significantly lower than that in healthy individuals. Besides, these results were consistent with findings reported by Obata et al., which demonstrated that the oxy-Hb concentration was lower in individuals after alcohol consumption[22]. Therefore, we concluded that the phenomenon is related to the neuroinhibitory effect of alcohol. Patients with alcohol dependence are conditioned to long-term alcohol consumption, which exerts a neurotoxic effect on the brain, leading to functional and structural changes in the central nervous system and causing cerebral blood flow hypoperfusion, cerebral blood oxygen saturation reduction, and long-term hypoxia in the brain[23]. In patients with alcohol dependence, sufficient oxygen is unavailable for neuronal activities during cognitive activities, and thus, oxygen consumption in the relevant brain regions activated by cognitive activities decreases, thereby reducing the relative concentration of oxy-Hb in the brain regions.

It is well established that alcohol affects human cognitive function. Rao et al. found that memory function in patients with alcohol dependence was severely impaired, with the significant impairment of transient and short-term memory[24]. Findings from several studies have confirmed that cognitive dysfunction related to mental illness is closely correlated with the relative concentration of oxy-Hb in the prefrontal lobe[25]. Pu et al. showed that the prefrontal blood flow and the relative concentration of oxy-Hb decreased significantly in patients with depression during the onset of the disease[26]. In this study, the executive function, memory function, and attention function in the observation group declined compared to that in the control, suggesting that patients with alcohol dependence showed impaired cognitive function. The results of Pearson's correlation analysis showed that the scores of correct responses, categories completed, BVMT-R, digital sequence test, digital span test, and CPT were positively correlated with the oxy-Hb concentration. Besides, the scores of responses administered, trials to compete first category, and perseverative response errors were negatively correlated with the oxy-Hb concentration. In addition, the concentration of oxy-Hb in the observation group was analyzed by the ROC curve, and the results showed that the oxy-Hb had high accuracy in the diagnosis of cognitive impairment caused by alcohol dependence.

The present study had certain limitations, including the fact that this was a single-center study with small sample size. Moreover, the years of alcohol dependence of patients were not included in the study, which may have led to a certain degree of difference in the brain function and structure as well as changes in the psychological behavior of patients. Besides, the evaluation of cognitive functions in patients with alcohol dependence was not comprehensive, and several other cognitive functions, such as decision-making, language, comprehension, judgment, and calculation, were not evaluated. Thus, a follow-up study with a large sample size is warranted.

In conclusion, we demonstrated that cognitive impairment occurs in patients with alcohol dependence, and the concentration of oxy-Hb in the prefrontal cortex of patients decreases compared to that in healthy people. This indicates that oxy-Hb detection can be a preliminarily determinant to suggest whether the cognitive function of patients with alcohol dependence is impaired.

Conflict of interests: the authors have no conflict of interests to declare.

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