

Short Communication

Effect of alcohol-dependence on cognitive performance in middle-aged men: Preliminary results

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ABSTRACT

Objectives: The understanding of the relationship between alcohol-related neuropathology, cognitive impairment, and various factors such as alcohol consumption, thiamine levels, and age vulnerability is still poorly understood. Therefore, this study aims to examine the effect of alcohol dependence on cognitive performance in middle-aged men with psycho-biochemical evidence.

Materials and Methods: A cross-sectional pilot study with a comparison group including 82 right-handed participants with and without alcohol dependence ($n = 41$ each). Alcohol dependence was diagnosed clinically by the International Classification of Disease Tenth Edition along with the use of alcohol use disorder identification test (AUDIT) and cognitive screening tests, that is, the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE). The serum levels of thiamine (Vitamin B1) were determined using an enzyme-linked immunosorbent assay.

Results: The MoCA scores, MMSE scores, and serum thiamine levels were significantly low for alcohol-dependent men (1509.43 ± 898.63 pmol/L) versus non-alcohol-dependent men (1862.81 ± 741.30 pmol/L; $P = 0.021$). The cognitive sub-domains including orientation, execution, calculation, visuocstructional skills, and recall functions were also significantly ($P < 0.05$) affected for the alcohol-dependent patients when compared to non-alcohol-dependent men. Serum thiamine levels showed a positive ($P < 0.05$) correlation with MoCA scores whereas serum thiamine levels showed a significant ($P < 0.05$) negative correlation with AUDIT scores.

Conclusion: Based on the significant positive association between serum thiamine levels with MoCA scores; therefore, both may be used as a screening tool for the early detection of cognitive impairment in patients with alcohol dependence.

Keywords: Thiamine, Alcohol dependence, Cognition, Mini-mental state examination, Montreal cognitive assessment, Neurotoxic

INTRODUCTION

Alcoholism is associated with brain damage and poor cognitive functioning.^[1] The alcohol-related neuropathology and cognitive impairment for different etiological factors, such as alcohol, thiamine levels, and age vulnerability show inconsistent evidence.^[1-3] This variation is due to methodological limitations^[4] in terms of study design, that is, population selection, age criteria, and a variety of neuropsychological tests measured. Few studies have also shown the effects of alcohol consumption on poor cognitive performance, particularly executive functions,^[5-11] episodic and working memory.^[10] In the present scenario, all clinicians use

subjective analysis to assess the cognitive status of alcohol-dependent patients. Further, the assessment of how rapidly cognition is progressing has important clinical implications. For this, a biological marker for rapid cognitive decline would be of importance because at-risk patients can be targeted early for non-pharmacological, medical, and psychosocial interventions to slow deterioration. Thiamine, also known as Vitamin B1, exerts neuroprotective^[6,9,12] effects by maintaining blood–brain barrier integrity and is particularly, studied as a biological marker for cognitive decline.^[13] To date, no published literature is available to show the association between thiamine blood levels and cognition in alcohol-dependent patients among the Indian middle-aged population. With this background, the present study was designed with the primary objective of evaluating the effect of alcohol dependence on neurocognitive functions using Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and cognitive biomarker-thiamine (Vitamin B1) levels among Indian middle-aged (36–55 years)^[4] men with alcohol dependence compared to non-alcohol dependent subjects. The secondary objective was to assess the correlation between the effect of alcohol dependence (alcohol use disorder identification test [AUDIT] scores) on the MoCA scores, MMSE scores, and serum thiamine levels and also provide a scientific association between the serum thiamine levels and MoCA scores.

MATERIALS AND METHODS

The present study was a cross-sectional pilot study with a comparison group including 82 right-handed, middle-aged (36–55 years) men with and without alcohol dependence ($n = 41$ each), carried out at a tertiary care hospital (All India Institute of Medical Sciences [AIIMS], Bathinda) in Western Punjab. This study was conducted by the Helsinki Declaration and was approved by the Institutional Ethics Committee (IEC) (Ref. No.: IEC/AIIMS/BTI/085; dated 17/03/2021). All participants provided written informed consent. The study was registered at the Clinical Trial Registry India (CTRI), CTRI/2021/12/039034. The study was conducted from September to November 2021 (the 2 months of the study period for the undergraduate Indian Council of Medical Research, New Delhi-STS-project 2020) in the Department of Psychiatry in association with the Department of Physiology and the Department of Biochemistry at AIIMS, Bathinda. The sample size for the study was calculated using n-master 2.0^[14] software assuming the prevalence^[15] of cognitive decline between 30% to 80% and 95% confidence interval with an absolute precision of 10% which came out to be 41 for each group.

Alcohol-dependent (Group A) participants were recruited on the basis of dependency on alcohol assessed by the International Classification of Disease Tenth Edition (ICD-10) criteria for diagnosis of alcohol dependence along with AUDIT.^[16] These patients came under F10 (alcohol withdrawal)

according to ICD-10 criteria. The inclusion criteria include those participants who were willing to participate in the study program after the detoxification phase of 7–10 days was over. The average years of alcohol consumption were found to be 11.36 ± 6.85 (mean \pm standard deviation) years. The exclusion criteria include patients with serious medical conditions, seriously sick, non-ambulatory, non-cooperative patients, with significant liver disease (cirrhosis of the liver), history of drug dependence other than nicotine or caffeine, clinical evidence of Wernicke–Korsakoff syndrome (WKS), a significant history of head trauma or brain surgery, organic brain syndrome, psychotic disorder, major depressive disorder, and bipolar disorder. Only clinical history was utilised to exclude other major psychiatric disorders.

An age-matched comparison group, Group B, that is, non-alcohol-dependent subjects was recruited from among the caregivers of patients attending the psychiatry outpatient department. The non-alcohol dependence was analysed on the basis of AUDIT scores. The subjects in the control group were non-alcohol dependent and few were social drinkers who were considered in Zone 1 based on the AUDIT scores according to the World Health Organisation (WHO) criteria.^[9,17,18] Exclusion criteria include those subjects having any serious medical problem or psychiatric illness on anamnestic recall, taking alcohol within 24 h of cognitive function assessment, a significant history of head trauma or brain surgery, history of drug dependence other than nicotine or caffeine. The aim of including the age-matched non-alcohol-dependent group was only to compare the natural variation in cognitive functions with the alcohol-dependent group.

We recorded sociodemographic data including age, height (stadiometer, Holtain Ltd., UK) body weight (digital weighing balance, Seca, Germany), body mass index (BMI), education level (<12 years, equal to 12 years and higher than 12 years)^[19] and family history of alcohol/drug use disorders through a family tree.

Cognitive assessments

All participants underwent cognitive assessment using the English and Hindi versions of MMSE and the MoCA in the present study. Both instruments were valid and reliable among Indians by taking cultural and linguistic differences into account.^[6] MMSE and MoCA were conducted within 5–10 min and 10–15 min, respectively, by the student under the supervision of expert clinicians.

MMSE

The MMSE^[20,21] is a 30-point questionnaire used extensively in clinical and research settings to measure cognitive impairment, including simple tasks in several areas: The test of time and place, the repeating lists of words, arithmetic such as serial subtractions of seven, language use and comprehension,

and basic motor skills. The scoring for MMSE includes (a) scores between 24 and 30 is no cognitive impairment; (b) scores between 18 and 23 is mild cognitive impairment and (c) scores between 0 and 17 is severe cognitive impairment.

MoCA

The MoCA^[22] is a brief 30-question questionnaire that helps to assess people for dementia. The 8.1 version of the MoCA test was translated into English provided by the MoCA test organisation (<http://www.MoCAtest.org/>). The MoCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: Attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The MoCA may be administered by anyone who understands and follows the instructions, however, only a health professional with expertise in the cognitive field may interpret the results. The total possible score is 30 points; a score of 26 or above is considered normal.

AUDIT questionnaire

The authors used the validated AUDIT^[16] which was developed by the WHO as a method of screening for alcohol dependence that includes alcohol consumption, drinking behaviour, and alcohol-related problems. AUDIT scores are interpreted as (a) 0–7 scores indicate low risk; (b) 8–15 scores indicate increasing risk; (c) 16–19 scores indicate higher risk and (d) 20 scores or more indicate possible dependence.

Estimation of cognitive biomarker

The concentration of serum levels of thiamine (Vitamin B1) was determined using a commercially available sandwich enzyme-linked immunosorbent assay kit (Immunotag, Geno Technology Inc., USA). Fasting venous blood samples (5 mL) were collected and allowed to clot for 10 min at room temperature and centrifuged at 2000–3000 rpm for 10 min. The serum was stored at –80°C until analysed. The limit of detection for Vitamin B1 levels ranged between 10 pmol/L and 4000 pmol/L. Quality control assays for biomarkers and validation were performed.

Statistical analysis

SPSS version 20.0 (IBM, Chicago, Illinois, United States of America, October 2020) was used for the statistical data analysis in this study. The normality of data was tested using the Kolmogorov–Smirnov test. The sociodemographic, MMSE scores, MoCA scores, serum Vitamin B1 levels, and cognitive sub-domains were analysed using the ‘Independent samples t-test’. The association between the AUDIT scores, MoCA Scores, MMSE Scores, and serum Vitamin B1 levels was evaluated using ‘Pearson Correlation Coefficient’. Significance was accepted at $P < 0.05$.

RESULTS

The present study included a total of 82 male participants with ($n = 41$) alcohol-dependent patients (age 41.72 ± 8.79 years) and ($n = 41$) non-alcohol-dependent subjects (age 43.34 ± 9.53 years) after meeting the inclusion and exclusion criteria [Table 1]. The alcohol-dependent patients had an average of 11.36 ± 6.85 years of alcohol consumption. No statistically significant differences were observed between alcohol-dependent and non-alcohol-dependent participants for age, education, BMI, systolic blood pressure, and diastolic blood pressure [Table 1].

Neurocognitive assessments

For neurocognitive functions, both MMSE (26.46 ± 2.08 ; 29.09 ± 1.23 ; $P = 0.001$) and MoCA scores (23.14 ± 2.70 ; 28.18 ± 1.64 ; $P = 0.008$), respectively, were found to be significantly less for the alcohol-dependent patients when compared with the non-alcohol-dependent group. Further, the serum Vitamin B1 (thiamine) levels were found to be significantly ($P = 0.021$) low for alcohol-dependent patients (1509.43 ± 898.63 pmol/L) versus non-alcohol-dependent subjects (1862.81 ± 741.30 pmol/L) [Table 1].

Correlations between the different neurocognitive tests

Further, the correlations between the different neurocognitive tests, that is, MoCA scores, MMSE scores, and Vitamin B1 (thiamine) levels with AUDIT scores were evaluated using the Pearson correlation coefficient. The MoCA scores ($r = -0.323$; $P = 0.039$) and Vitamin B1 levels ($r = -0.460$; $P = 0.002$) had a significant negative correlation with AUDIT scores in middle-aged men with alcohol dependence [Figures 1a and b]. However, the MMSE scores were negatively correlated with AUDIT scores but no statistical significance ($r = -0.215$; $P = 0.176$) was observed between them. Importantly, the present study observed a significant ($r = 0.550$; $P = 0.01$) positive correlation between serum thiamine levels with MoCA scores [Figure 2].

Sub-scores of cognitive domains assessed by MMSE and MoCA

Based on the distribution of each cognitive domain sub-score in total samples assessed by different items of MMSE and MoCA [Table 2]. The performance of orientation, execution, naming, registration, visuoconstructional skills, writing, and repetition was found to be significantly ($P < 0.05$) decreased in alcohol-dependent patients versus non-alcohol-dependent group using MMSE maximum scores; whereas orientation, execution, calculation, visuoconstructional skills and recall functions were found to be significantly ($P < 0.05$) decreased in alcohol-dependent patients versus non-alcohol-dependent group using MoCA test. Importantly, calculation, recall, visuoconstructional skills, and writing are affected in alcohol-dependent patients more significantly ($P < 0.05$) than non-alcoholic-dependent subjects.

DISCUSSION

To the best of our knowledge, this is the first report from the Indian population providing psycho-biochemical evidence that cognitive functions deteriorate in middle-aged men with alcohol dependence. Further, the present study also focussed on the sub-analysis of the cognitive

domains of MMSE and MoCA. It has been observed that calculation, recall, visuoconstructional skills, and writing are significantly affected more in our study population when compared with other study research findings.^[10,23,24] This impairment in cognitive performance of sub-domains may be due to the alcohol addiction process that affects the thiamine metabolism^[6,9,12] and leads to neurotoxicity which

Table 1: Demographic data and clinical parameters for study participants.

Parameters	Mean ±SD		p-value
	Alcohol-Dependent Group (n=41)	Healthy control Group (n=41)	
Demographic Data			
Age (years)	41.72 ± 8.79	43.34 ± 9.53	0.55
Body Mass Index (Kg/m ²)	24.66 ± 3.55	24.19 ± 3.22	0.56
Education n, (%)			
<12 years	19 (46.3%)	09 (21.9%)	0.10 (4.10) [*]
12 years	15 (36.6%)	25 (61.0%)	
>12 years	07 (17.1%)	07 (17.1%)	
Systolic Blood Pressure (SBP) (mmHg)	126.64 ± 13.96	124.07 ± 8.21	0.17
Diastolic Pressure (DBP) (mmHg)	84.66 ± 9.74	81.84 ± 4.55	0.10
AUDIT Scores (Alcohol dependence questionnaire scores)	20.26 ± 9.01	3.1 ± 1.4	0.001
Neurocognitive Examinations			
MMSE Score	26.46 ± 2.08	29.09 ± 1.23	0.001
MoCA Score	23.14 ± 2.70	28.18 ± 1.64	0.008
Serum Thiamine (Vitamin B1) Levels (pmol/L)	1509.43 ± 898.63	1862.81 ± 741.30	0.021
All values are in mean±SD (standard-deviation); 'n'= Number of study participants; p=Independent t-test between alcohol-dependent group vs. healthy control group Categorical data=chi-square test [*] These bold p-value are statistically significant (p<0.05). MoCA: Montreal Cognitive Assessment MMSE: Mini-Mental State Examination, SD: Standard Deviation			

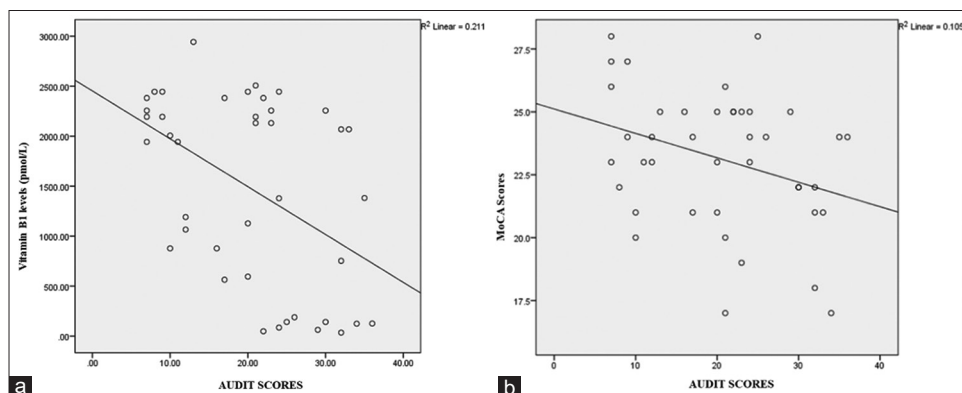


Figure 1: (a) Correlation of alcohol dependence identification test (AUDIT) scores on thiamine (Vitamin B1) levels in alcohol-dependent patients, (b) correlation of alcohol use disorder identification test (AUDIT) scores on Montreal Cognitive Assessment (MoCA) scores.

Table 2: Cognitive sub-domain analysis of MMSE and MoCA scores for Groups A and B participants.

Domains	Items/maximum scores	MoCA: Montreal Cognitive Assessment (Mean ±SD)		p-value
		Alcohol-Dependent Group (n=41)	Non-alcohol-Dependent Group (n=41)	
Orientation	Orientation to time and place/6	5.88 ± 0.38	6.00 ± 0.00	0.05
Executive function	Trail-making test/1	0.75 ± 0.43	0.77 ± 0.42	0.80
	Digit span test/2	1.71 ± 0.54	1.91 ± 0.28	0.03
	Verbal fluency/1	0.53 ± 0.50	0.80 ± 0.40	0.07
	Abstraction test/2	1.84 ± 0.47	2.00 ± 0.21	0.04
Calculation	Serial 7 subtractions/3	2.28 ± 1.10	2.95 ± 0.20	0.001
Naming	Naming (lion, giraffe, camel)/3	2.82 ± 0.38	2.91 ± 0.28	0.21
Repetition	2 longer sentences/2	1.35 ± 0.57	1.53 ± 0.58	0.14
Visuoconstructional skills	Copy cube/1	0.48 ± 0.50	0.77 ± 0.42	0.004
	Draw clock face/3	2.13 ± 0.69	2.33 ± 0.60	0.14
Attention	Vigilance test for number '1'/1	0.88 ± 0.31	0.93 ± 0.25	0.46
Recall	Recall 5 words/5	2.13 ± 1.42	3.40 ± 0.86	0.001

Domains	Items/maximum scores	MMSE: Mini-Mental State Examination (Mean ±SD)		p-value
		Alcohol-Dependent Group (n=41)	Healthy Control Group (n=41)	
Orientation	Orientation to time and place/10	9.35 ± 0.90	9.88 ± 0.31	0.001
Executive function	Repeat 3 words/3	2.42 ± 0.65	2.53 ± 0.62	0.41
	Reading command test/1	0.86 ± 0.34	1.00 ± 0.00	0.01
Calculation	Serial 7 subtraction/5	4.35 ± 1.11	4.68 ± 0.59	0.08
Naming	Naming (pencil, watch)/2	1.71 ± 0.58	2.00 ± 0.00	0.01
Registration	Repeat 3 words/3	2.86 ± 0.40	3.00 ± 0.00	0.03
Recall	Recall 3 words/3	2.28 ± 0.69	2.40 ± 0.57	0.41
Visuoconstructional skills	Copy intersecting pentagons/1	0.82 ± 0.38	1.00 ± 0.00	0.03
Writing	Write a sentence/1	0.71 ± 0.45	0.93 ± 0.25	0.005
Repetition	1 short sentence/1	0.68 ± 0.46	0.86 ± 0.34	0.04

All values are in mean±SD; p=Independent t-test between alcohol-dependent group vs. control group; 'n'= Number of study participants. These bold p-value are statistically significant (p<0.05).
 MoCA: Montreal Cognitive Assessment
 MMSE: Mini-Mental State Examination, SD: Standard Deviation

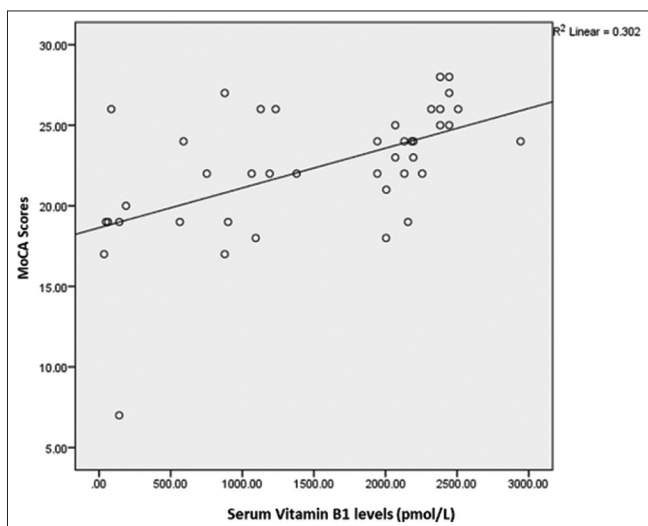


Figure 2: Correlation of Vitamin B1 levels with Montreal Cognitive Assessment (MoCA) scores in alcohol-dependent patients.

further affects the brain areas, especially shrinkage of the hippocampal region.^[25]

The previous research findings observed the uncertainty in the association between alcohol drinking and cognitive dysfunctions. Some studies have found no association between alcohol drinking and cognitive impairment^[26,27] or Alzheimer's disease,^[28] whereas others have found an association between heavy drinking and increased risk of dementia.^[26,27,29] Some have claimed there is a J or U-shaped relation between alcohol drinking and cognitive impairment^[2,4,10,13] or dementia^[7,8,13] Importantly, these studies showed inconsistency in their findings due to the methodological limitations in terms of study design about population selection, age criteria and a variety of neuropsychological tests used and did not validate it by any clinical or diagnostic criteria for defining the mild cognitive impairment.^[4] For this, the present study has also provided the associations between alcohol dependency with different neuropsychological tests. We observed a non-linear relationship between alcohol dependency (AUDIT scores) with cognitive tests, that is, MoCA scores. Importantly, serum thiamine levels showed a linear relationship with MoCA cognitive scores. This linear relationship provides the scientific affirmation that cognitive domains are affected due to a decrease in serum

thiamine levels. Reduced cellular thiamine concentrations, combined with the toxic effects of ethanol and acetaldehyde, are considered crucial factors contributing to cognitive impairment among individuals with alcohol dependence and also heighten the risk of developing WKS. This finding provides the scientific platform for the need for early detection of cognitive decline.

Strengths and limitations of the study

The present comparative cross-sectional study in India provided psycho-biochemical evidence to show the impact of alcohol dependence on different cognitive domains in middle-aged men. The study also strengthened its findings by establishing correlations between MoCA scores and serum thiamine levels with AUDIT scores. In addition, the linear association of serum thiamine levels with MoCA scores provides scientific validity to affirm the early detection of cognitive decline in alcohol-dependent patients. In the present scenario, all clinicians use subjective analysis to assess cognitive status. Therefore, this study also tries to bring the superiority in the use of cognitive biomarkers, that is, serum thiamine levels along with MoCA scores rather than solely relying on subjective neurocognitive test MoCA for cognitive decline. Sub-domain analysis of the MoCA also revealed interesting trends, indicating that alcohol-dependent patients exhibited a more significant decline in the calculation, visuoconstructional skills, and recall domain when compared to the non-alcohol-dependent group. This study group comprised middle-aged men who were specifically selected for cognitive assessment so that potential pharmacological and non-pharmacological interventions could be done to effectively prevent cognitive decline in their future as they age. Further, longitudinal studies are warranted to understand the association between different cognitive domains with serum thiamine levels in alcohol-dependent populations.

Although the study was conducted with a relatively sound methodology, this study nonetheless has a few limitations. First, due to the small sample size, the findings of this study need to be corroborated in larger sample studies because the study being time-bound short-term research for undergraduate students (2 months) could not afford a larger sample. Second, only male subjects were recruited for the study. There were no firm criteria to exclude female patients but no reported case of females with alcohol dependence was found in the small district. Third, the percentage decrease in serum thiamine levels for the number of years of alcohol intake could not be carried out to assess the rate of cognitive decline in alcohol-dependent patients. Further, the diet assessment could not be carried out for the alcohol-dependent patients to provide a better explanation of the cognitive decline. Furthermore, the effect of nicotine on thiamine levels could not be carried out for the data analysis. Despite these limitations, the present findings provide

psycho-biochemical evidence to aware alcohol-dependent patients aware of their cognitive status.

CONCLUSION

Based on the significant positive association between serum thiamine levels with MoCA scores, both may be used as a screening tool for the early detection of cognitive impairment in patients with alcohol dependence.

Author Contributions

Pankhita Ghai was involved in the study conduct and acquiring the data; Dipti Magan was involved in study conceptualization, study design, data analysis, data interpretation, writing of the manuscript, and approving the final content of the manuscript; Jitender Aneja was involved in data analysis, data interpretation and manuscript review; Himanshu Sharma was involved in the biochemical estimation of cognitive biomarker and manuscript review; Aarthi Choudhary was involved in assisting the student for data collection.

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Ethical approval

This study was conducted by the Helsinki Declaration and was approved by the Institutional Ethics Committee (IEC) (Ref. No.: IEC/AIIMS/BTI/085; dated 17/03/2021).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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