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Age-related cognitive decline is accelerated in alcohol use disorder

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Abstract

This study aimed to examine potential cognitive impairments in patients with alcohol use disorder (AUD), and explore the factors affecting them. We recruited 97 inpatients with AUD, showing superficially normal cognitive function (mini-mental state examination score ≥24) for this study. We assessed cognitive function after a 4-week post-abstinence period using the Brief Assessment of Cognition in Schizophrenia-Japanese version (BACS-J). Relationships between BACS-J subcategory/composite raw scores and *Z*-scores (deviation from standard data in healthy Japanese) and background factors such as age, sex, education, smoking status, mini-mental state examination score, body mass index, systolic blood pressure, severity of depression, alcohol consumption, and laboratory findings were analyzed. Multiple regression analysis showed that the age ($p < 0.001$) and total bilirubin level ($p = 0.014$) were worsening factors for the BACS-J composite raw score, whereas education ($p < 0.001$) was a protective factor. An inverse correlation was apparent between the age and the composite *Z*-score of the BACS-J ($r = -0.431$, $p < 0.001$). Receiver operating characteristic (ROC) analysis identified 53 years as the cutoff age for predicting more than −2SD cognitive decline from the normal standard, with a high negative predictive value (95%). Patients with AUD aged ≥53 years showed more pronounced impairments in verbal memory, working memory, verbal fluency, and attention than those younger than 53 years ($p < 0.05$). These findings clearly demonstrate accelerated age-related cognitive decline in patients with AUD, especially those aged ≥53 years, suggesting the necessity of early intervention in patients with AUD to prevent progressive cognitive impairment and preserve their quality of life.

KEYWORDS
age-related cognitive decline, alcohol use disorder, brief assessment of cognition in schizophrenia—Japanese version, cognitive impairment, dementia

1 | INTRODUCTION

Extensive research has shown that heavy and repeated alcohol consumption can increase the risk of future cognitive deterioration.[1] Korsakoff syndrome is a critical manifestation of cognitive dysfunction within the spectrum of alcohol use disorder (AUD)[2] and is often precipitated primarily by protracted thiamine insufficiency. This deficit is frequently associated with excessive and chronic alcohol consumption. In addition, the emergence of a pathology known as alcohol-related dementia (ARD), an additional variant of cognitive debilitation intrinsically linked to long-standing severe alcohol intake,[3] has diverse harmful effects on the brain.

Current research has also focused on mild cognitive impairment associated with AUD.[4] The hypothesis that alcohol can cause premature aging,[5] potentially leading to early onset dementia, has garnered increasing attention. Therefore, cognitive impairment in patients with AUD (even though they have subtle and late manifestations) may require advanced examination[6] at the early stage of the inconspicuous but potentially progressive course.[7] Cognitive deficits in patients with AUD have been reported across various cognitive domains, including general memory,[8] working memory,[9] processing speed,[10] verbal fluency,[11] and executive function.[12]

The neurotoxic effects of alcohol, which manifest prominently as structural changes such as cerebral atrophy,[13] are well substantiated in the literature. Contemporary research has further elucidated the brain lesions responsible for such cognitive impairments, implicating specific disruptions in neural areas such as the orbitofrontal and dorsolateral prefrontal cortices[14] and dorsolateral prefrontal cortex.[15] Impairment of prefrontal function significantly affects the adaptive behavior,[16] quality of life (QOL),[17] decision-making abilities,[18] and active participation in treatment.[19]

It is common to encounter mild cognitive impairment in individuals with AUD receiving ongoing treatment in the usual clinical setting.[20] This underlines the indispensable role of routine cognitive assessment in the optimization of therapeutic outcomes for these patients. However, clinicians have underestimated and paid little attention to the possible existence of cognitive impairments associated with AUD.[21] Despite recent attempts to develop swift and detailed assessments of cognitive function,[22] routine cognitive assessments have not been incorporated into clinical practice. The development of rapid and clinically applicable battery tests specific for AUD is therefore required to gain a comprehensive understanding of potential cognitive impairment in patients with AUD.[23]

The Brief Assessment of Cognition in Schizophrenia (BACS) was developed as a standard neurocognitive battery for schizophrenia.[24] The BACS, a swift and convenient instrument, enables the comprehensive appraisal of various cognitive subcategories such as verbal memory, working memory, motor speed, verbal fluency, attention, and executive function. The Japanese version of the BACS (BACS-J) has been validated and shown to provide reliable data for Japanese populations,[25] enabling the calculation of Z-scores as deviations from normal standards in each generation of healthy Japanese individuals.[26] Although BACS was originally developed for schizophrenia, its use has gradually been extended to other psychiatric conditions, including mood disorders.[27]

Accordingly, to investigate detailed cognitive functions, we applied the BACS-J to Japanese patients with AUD in the present study. To the best of our knowledge, this is the first BACS trial to comprehensively assess cognitive function in patients with AUD. Therefore, this study aimed to identify potential cognitive impairments and clarify their profiles, together with further exploration of various background factors affecting cognitive function in patients with AUD.

2 | METHODS

2.1 | Participants

The study sample consisted of adult inpatients admitted to the National Hospital Organization Ryukyu Hospital between March 2018 and March 2020. Of the 125 patients initially approached, 117 (93.6%) provided consent to participate. The diagnosis of AUD was confirmed by two experienced psychiatrists based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.[28] We excluded patients with a diagnosis of dementia based on DSM-5 (including those with Alzheimer's disease or cerebrovascular dementia), with a potential diagnosis of Wernicke–Korsakoff syndrome, or with a Mini-Mental State Examination (MMSE)[29] score of <24 upon admission. Ultimately, we included 97 patients (MMSE ≥24) without apparent organic brain syndrome. Among the participants with AUD diagnosis, four were treated with benzodiazepine anxiolytics, seven with antidepressants, eight with antipsychotics, and one with anticholinergics.

2.2 | Measures

We collected demographic data (age, sex, years of education, smoking status, and the body mass index) upon admission. Cognitive function was initially screened using the MMSE to exclude potential participants with severe cognitive impairment based on the irreversible process of organic brain disturbance. The severity of alcohol dependence was evaluated using the Alcohol Use Disorders Identification Test (AUDIT),[30] which measures subcategories including hazardous alcohol use, dependence symptoms, and harmful alcohol use. Laboratory tests were conducted to assess total cholesterol, hemoglobin A1c, albumin, total bilirubin, blood urea nitrogen (BUN), vitamin B1, and folic acid levels. Regarding cognitive decline in patients with AUD, we consider that their long-term living and metabolic conditions play a pivotal role. Thus, we assumed that the admission data to closely reflected their recent lifestyle and health conditions. Additionally, we selected the HbA1c and T-Bil tests for their consistent stability and representation of long-term glycemic control and liver function. The mean systolic blood pressure was obtained from three separate measurements obtained during inpatient treatment. To ensure stable readings, these

measurements were performed during post withdrawal treatment, starting on the 10th day after admission.

The BACS-J was administered to measure cognitive function after 4 weeks of alcohol abstinence to reduce the potential confounding effects of alcohol withdrawal. The BACS-J assesses verbal memory, working memory, motor speed, verbal fluency, attention, and executive function. The composite BACS-J raw score was defined as the average raw score for each subcategory. Age- and sex-adjusted *Z*-scores were calculated for each BACS-J subcategory using normative data from a previous study.[26] The composite *Z*-scores were then calculated as the mean of the adjusted *Z*-scores across the subcategories. Furthermore, the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR)[31] was administered concurrently with the BACS-J to explore potential associations with depressive symptoms.

2.3 | Statistical analyses

Multiple regression analysis was used to identify factors affecting both the composite BACS-J raw scores and their subcategory scores. Pearson's correlation coefficient was used to evaluate the relationship between age and the composite raw score/*Z*-score of the BACS-J. The ROC curve was plotted to identify the cutoff age that maximized the area under the curve (AUC) corresponding to the composite *Z*-score of the BACS-J as two standard deviations below the normal standard. Based on this cutoff, the age- and sex-adjusted subcategories and composite *Z*-scores of the BACS-J were compared between the two age groups (<cutoff and ≥cutoff) with AUD. Statistical significance was set at $p < 0.05$ (two-tailed). Statistical analyses were performed using the Statistical Package for the Social Sciences software version 28.0.0.0 J for Windows (SPSS Japan, Tokyo, Japan).

2.4 | Ethics procedures

The research protocol for this study was reviewed and approved by a duly constituted Ethics Committee, conforming to the provisions of the Declaration of Helsinki. The Ethics Committee of the National Hospital Organization Ryukyu Hospital granted approval, under Approval no. 29–21. All study participants provided written informed consent prior to their participation. Data were anonymized for analysis purposes. Participants were informed about the objective of the study, the measures taken to ensure the confidentiality of their personal information, and their right to withdraw from the study at any time.

3 | RESULTS

The background and laboratory findings of the 97 patients with AUD are summarized in Table 1. The mean age of the participants was 47.4 ± 10.4 years. The percentage of males was 85.6%, and that of females 14.4%. Other parameters (mean ± SD, or %) were as follows: education, 11.8 ± 2.0 years; current smokers, 81.4%; MMSE score, 27.2 ± 2.1; body mass index, 23.0 ± 4.6 kg/m^2; systolic blood pressure, 122.2 ± 15.8 mmHg; total cholesterol, 207.4 ± 61.8 mg/dL; albumin, 4.2 ± 0.7 g/dL; total bilirubin, 1.5 ± 1.4 mg/dL; BUN, 9.9 ± 4.4 mg/dL; vitamin B1, 52.4 ± 43.7 ng/mL; and folic acid, 9.7 ± 23.2 ng/mL. Regarding glycemic control, 14.4% had an HbA1c level ≥6.5%. Concerning the severity of depression and AUD, the QIDS-SR score was 6.2 ± 4.3, the AUDIT total score was 27.5 ± 6.3, and the AUDIT subcategory scores were as follows: hazardous alcohol use, 11.0 ± 1.6; dependence symptoms, 6.4 ± 3.8; and harmful alcohol use, 10.1 ± 2.9.

TABLE 1 Clinical data and laboratory findings in 97 patients with alcohol use disorder.

Age: Years (mean ± SD)	47.4 ± 10.4
Sex	
Male: *n* (%)	83 (85.6)
Female: *n* (%)	14 (14.4)
Education: years (mean ± SD)	11.8 ± 2.0
Current smoker: *n* (%)	79 (81.4)
MMSE Score	27.2 ± 2.1
Body mass index: kg/m^2 (mean ± SD)	23.0 ± 4.6
Systolic blood pressure: mmHg (mean ± SD)	122.2 ± 15.8
Total cholesterol: mg/dL (mean ± SD)	207.4 ± 61.8
HbA1c (NGSP)	
<6.5: *n* (%)	83 (85.6)
≥6.5: *n* (%)	14 (14.4)
Albumin: g/dL (mean ± SD)	4.2 ± 0.7
Total bilirubin: mg/dL (mean ± SD)	1.5 ± 1.4
BUN: mg/dL (mean ± SD)	9.9 ± 4.4
Vitamin B1: ng/mL (mean ± SD)	52.4 ± 43.7
Folic acid: ng/mL (mean ± SD)	9.7 ± 23.2
QIDS-SR (mean ± SD)	6.2 ± 4.3
AUDIT Score (mean ± SD)	27.5 ± 6.3
Hazardous alcohol use (mean ± SD)	11.0 ± 1.6
Dependence symptoms (mean ± SD)	6.4 ± 3.8
Harmful alcohol use (mean ± SD)	10.1 ± 2.9

Note: "Hazardous alcohol use", "Dependence symptoms", and "Harmful alcohol use" are subcategories of the AUDIT. They correspond to AUDIT questions 1–3, 4–6, and 7–10, respectively.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BUN, Blood urea nitrogen; HbA1c, Hemoglobin A1c; MMSE, Mini Mental State Examination; SD, standard deviation; QIDS-SR, The Quick Inventory of Depressive Symptomatology (Self-Report).

Multiple regression analysis for the prediction of the composite raw score of the BACS-J revealed that age ($\beta = -0.536$, $p < 0.001$) and total bilirubin level ($\beta = -0.213$, $p = 0.014$) were worsening factors for the BACS-J raw score, while education ($\beta = 0.324$, $p < 0.001$) was a protective factor (Table 2). This model accounted for 50.7% of the variance (adjusted $R^2 = 0.465$; $F = 5.904$; $p < 0.001$).

TABLE 2 Multiple regression analysis for factors predicting the composite raw score of the Brief Assessment of Cognition in Schizophrenia Japanese version (BACS-J).

Predictors	*B*	Std. error	*β*	*p*-Value
Constant	39.385	9.041		<0.001*
Age: years	−0.364	0.059	−0.536	<0.001*
Sex: male	−0.952	1.752	−0.048	0.588
Education: years	1.143	0.301	0.324	<0.001*
Current smoker	1.771	1.494	0.098	0.239
Body mass index: kg/m^2	−0.021	0.121	−0.014	0.862
Systolic blood pressure: mmHg	−0.008	0.037	−0.018	0.830
Total cholesterol: mg/dL	−0.002	0.009	−0.014	0.862
HbA1c ≥6.5 (%)	−0.812	1.625	−0.041	0.619
Albumin: g/dL	0.885	0.848	0.089	0.300
Total bilirubin: mg/dL	−1.052	0.417	−0.213	0.014*
BUN: mg/dL	−0.057	0.135	−0.036	0.675
Vitamin B1: ng/mL	−0.003	0.013	−0.019	0.816
Folic acid: ng/mL	−0.023	0.024	−0.074	0.355
QIDS-SR	−0.099	0.123	−0.070	0.422
Hazardous alcohol use (AUDIT Q1 ~ Q3)	0.142	0.371	0.032	0.703
Dependence symptoms (AUDIT Q4 ~ Q6)	0.225	0.173	0.120	0.196
Harmful alcohol use (AUDIT Q7 ~ Q10)	−0.044	0.223	−0.018	0.844
R = 0.748	Adjust R^2 = 0.465	F = 5.904	p < 0.001*	

Note: B, unstandardized coefficient; *β*, standardized coefficient.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; Std. error, standard error; BUN, blood urea nitrogen; HbA1c, Hemoglobin A1c; QIDS-SR, The Quick Inventory of Depressive Symptomatology (Self-Report).

*p-value <0.05.

On the other hand, no significant differences were observed for other factors. Additionally, we statistically evaluated the impact of medications such as benzodiazepine anxiolytics, antidepressants, antipsychotics, and anticholinergics, and found no significant differences.

Table 3 shows the results of multiple regression analyses for predicting the subscale scores of the BACS-J. Age was a significant predictor across several subscales, showing negative associations with verbal memory ($\beta = -0.544$, $p < 0.001$), motor speed ($\beta = -0.299$, $p = 0.07$), verbal fluency ($\beta = -0.332$, $p = 0.02$), attention ($\beta = -0.479$, $p < 0.001$), and executive function ($\beta = -0.373$, $p < 0.001$). Education showed a positive association with performance in the verbal memory ($\beta = 0.268$, $p = 0.007$), verbal fluency ($\beta = 0.226$, $p = 0.027$), and attention ($\beta = 0.302$, $p = 0.02$) subscales. Total bilirubin levels negatively influenced the working memory ($\beta = -0.225$, $p = 0.038$) and attention ($\beta = -0.315$, $p = 0.01$) subscales, while albumin levels positively influenced motor speed ($\beta = 0.215$, $p = 0.048$). BUN had a negative impact on the verbal fluency subscale ($\beta = -0.224$, $p = 0.027$). The QIDS-SR score showed a negative association with the working memory subscale ($\beta = -0.222$, $p = 0.046$).

Figure 1 shows the inverse correlation of age with the composite raw score ($r = -0.623$, $p < 0.001$) and the Z-score of the BACS-J ($r = -0.431$, $p < 0.001$). In particular, the latter correlation indicates that age-related cognitive decline is accelerated in patients with AUD compared to the normal population.

The ROC analysis identified 53 years as the cutoff age for predicting more than −2SD cognitive decline from the normal standard, with an AUC value of 0.80 (Figure 2), yielding an excellent negative predictive value (95%) and modest but sufficient sensitivity (75%) and specificity (73%). When the subjects were divided into two age groups (<53 and ≥53 years), the older age group showed more pronounced impairments in verbal memory, working memory, verbal fluency, and attention than the younger age group (Figure 3).

4 | DISCUSSION

Although demographic profiles of AUD differ among countries with various sociocultural backgrounds, maturity of healthcare infrastructure, and patterns of alcohol consumption, the characteristics of our samples in the present study (Table 1) seem to be almost representative of Japanese patients with AUD, commonly showing late forties to early fifties as the median generation, male-dominant gender distribution, and a relatively short education period, as described in a previous report on Japanese patients with AUD.[32]

TABLE 3 Multiple regression analyses for the prediction of subscale scores of the Brief Assessment of Cognition in Schizophrenia Japanese version (BACS-J).

Predictors	Verbal memory	Working memory	Motor speed	Verbal fluency	Attention	Executive function
Age: years	β (−0.544) ***	—	β (−0.299) **	β (−0.332) **	β (−0.479) ***	β (−0.373) ***
Sex: male	—	—	—	—	—	—
Education: years	β (0.268) **	—	—	β (0.226) *	β (0.302) **	—
Current smoker	—	—	—	—	—	—
Body mass index: kg/m^2	—	—	—	—	—	—
Systolic blood pressure: mmHg	—	—	—	—	—	—
Total cholesterol: mg/dL	—	—	—	—	—	—
HbA1c ≥6.5 (%)	—	—	—	—	—	—
Albumin: g/dL	—	—	β (0.215) *	—	—	—
Total bilirubin: mg/dL	—	β (−0.225) *	—	—	β (−0.315) **	—
BUN: mg/dL	—	—	—	β (−0.224) **	—	—
Vitamin B1: ng/mL	—	—	—	—	—	—
Folic acid: ng/mL	—	—	—	—	—	—
QIDS-SR	—	β (−0.222) *	—	—	—	—
Hazardous alcohol use (AUDIT Q1 ~ Q3)	—	—	—	—	—	—
Dependence symptoms (AUDIT Q4 ~ Q6)	—	—	—	—	—	—
Harmful alcohol use (AUDIT Q7 ~ Q10)	—	—	—	—	—	—
Adjusted R^2	0.296	0.147	0.167	0.263	0.346	0.165

Note: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. "—" indicates no significant difference.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BUN, blood urea nitrogen; HbA1c, Hemoglobin A1c; QIDS-SR, The Quick Inventory of Depressive Symptomatology (Self-Report); β, standardized coefficient.

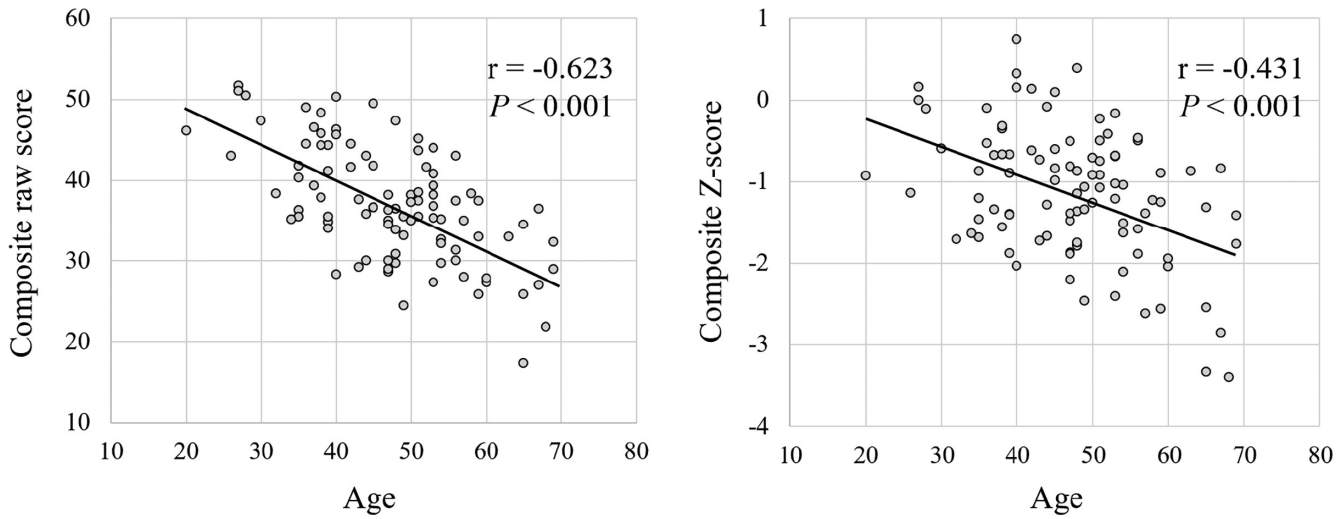

FIGURE 1 Correlations between the age and composite raw score (left panel) or the Z-score (right panel) of the Brief Assessment of Cognition in Schizophrenia Japanese version (BACS-J) in 97 patients with alcohol use disorder.

The mean MMSE score (27.2) of our participants did not demonstrate any clinically apparent cognitive disturbances (Table 1). Concerning metabolic markers and laboratory findings, such as the BMI, systolic blood pressure, and cholesterol, albumin, BUN, vitamin B1, and folic acid levels, our samples appeared to be within the standard ranges. The prevalence of abnormal HbA1c (≥6.5%) in our participants (14.4%) is almost comparable to the data in the 2016 National Health and Nutrition Survey in Japan (12.2%).[33] These findings partly suggest that predominant metabolic/vascular diseases and vitamin B1 deficiency did not affect

cognitive function in our patients with AUD. Although the mean QIDS-SR score was slightly higher than the cutoff score of 6, it is natural that an apparently high AUDIT score (27.5 on average) drew the most attention as a cause of cognitive decline in patients with AUD. Therefore, our demographic data suggest that only abnormal alcohol intake is likely responsible for cognitive decline in patients with AUD.

Although robust deterioration in cognition was not evident from the MMSE scores in our patients with AUD, the BACS revealed general impairments in attention, working memory, motor speed, and executive function (Figures 1 and 3). Presumably, the severity is almost comparable to bipolar disorder or schizophrenia, according to previous data on the BACS in various psychiatric disorders, although the pattern of impaired cognition is not specific to AUD.[34] Such cognitive decline can affect social and daily life functioning, as well as QOL and prognosis in patients with AUD.

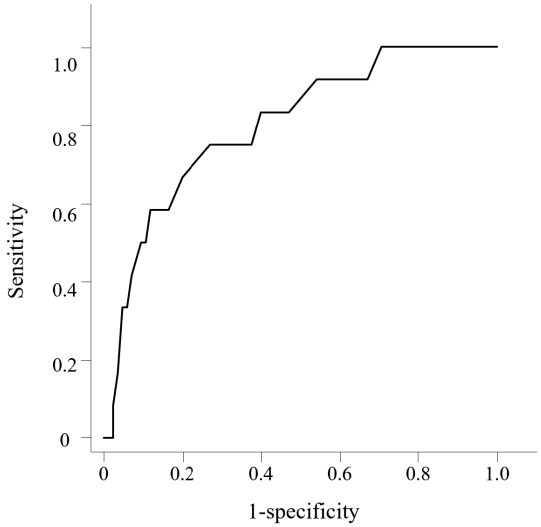

FIGURE 2 ROC curve distinguishing −2SD of the composite Z-score of the Brief Assessment of Cognition in Schizophrenia Japanese version (BACS-J) with a cutoff age of 53 years. Area under the curve = 0.80, sensitivity 75%, specificity 73%, positive predictive value 28%, and negative predictive value 95%.

Among patients with AUD, age was the most potent factor accelerating cognitive impairment, as manifested by the greatest negative β-value (−0.536; Table 2) and the strong negative correlation between the age and the composite raw scores of the BACS-J (Figure 1). This result is partly supported by previous literature, establishing accelerated aging in patients with AUD as a general fact.[35] However, it is surprising that age should play such a crucial role in the cognitive decline of patients with AUD. Clinicians should be more careful about the synergistic effects of aging and chronic alcohol consumption on the drastic deterioration in the cognitive function of patients with AUD.

Total bilirubin levels contributed to cognitive decline in patients with AUD (Table 2), which is in agreement with previous studies.[36] Alcoholic liver injury is a partially reversible and treatable pathology, and it appears to be less important as a risk factor compared to age. On the other hand, education protected against cognitive impairment in patients with AUD (Table 2). Education is a well-recognized protective factor against cognitive impairment.[37] However, clinicians should be aware of the unavoidable fact that a lower educational level is a core characteristic of patients with AUD. Regarding the AUD subscales, they showed no significant effects. It is worth noting that our study primarily focused on patients with severe AUD requiring hospitalization. The inclusion of regular drinkers or patients with mild AUD in the study might have revealed an additional effect of alcohol consumption frequency and quantity.

Based on the results from Table 3, age prominently influences the cognitive parameters assessed by the BACS-J, showing in particular a negative association across several subscales such as verbal memory, motor speed, verbal fluency, attention, and executive function. This extensive effect emphasizes the profound influence of aging

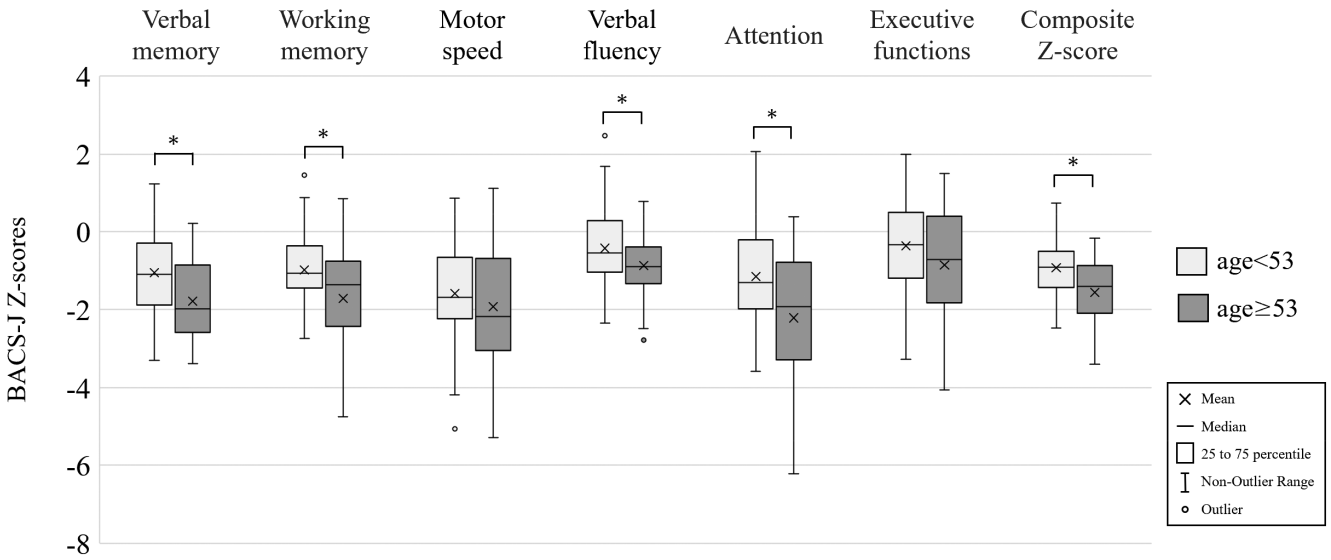

FIGURE 3 Comparisons of subcategory Z-scores and the composite Z-score of the Brief Assessment of Cognition in Schizophrenia Japanese version (BACS-J) between the two age groups (<53 and ≥53) with alcohol use disorder. *p-value <0.05.

on cognition. Apart from age, other factors such as total bilirubin levels (affecting working memory and attention), BUN (affecting the verbal fluency), and QIDS-SR scores (affecting the working memory) were also noted to adversely impact cognitive function. However, the influence of these factors was limited when compared to that of age, which consistently emerged as the primary determinant and impacted a broad range of cognitive domains.

Although the *Z*-scores of the BACS-J were adjusted for age and sex in the Japanese population, they significantly decreased as age increased in patients with AUD (Figure 1), suggesting that these patients show more progressive cognitive decline with aging than the normal population. In particular, 53 years of age seems to be the critical age for severe (−2SD decline from the normal standard) and probably irreversible degradation of cognition (Figure 2). In particular, declines in verbal memory/fluency, working memory, and attention were more apparent in patients at 53 years of age or older, compared to younger patients (Figure 3). Furthermore, the average lifespan reported for patients with AUD falls within the early fifties.[37] Interestingly, the age of 53 emerged in our study as a significant threshold for cognitive decline in patients with AUD. This cognitive impairment might hinder their capabilities for self-management, potentially compromising their daily functioning. Thus, the detrimental effects of alcohol on the lifespan of the individual might not only be due to its physical consequences but also due to the associated decline in cognitive functions.

Meanwhile, an excellent negative predictive value (95%) at 53 years of age suggests a low probability of significant cognitive impairment in individuals under 53 years of age (Figure 2). This may imply that early intervention before the critical age is warranted to preserve cognitive levels in patients with AUD. However, a substantial proportion of middle-aged individuals with AUD around the aforementioned critical age exist in Japan.[38] Therefore, we should be aware of the short period left for treatment interventions to halt the progression of cognitive decline in patients with AUD.

Denial is a predominant psychological profile in patients with AUD and often interferes with the initial treatment for the syndrome. In contrast, preserved cognitive function followed by sustained QOL may serve as a potent motive for the continuation of AUD treatment. However, it may be difficult to expect the use of such internal resources in patients with AUD in their late fifties. Physical, psychological, and social recovery from AUD must be completed far before the critical age, as basic cognitive capability is a prerequisite for alcohol rehabilitation programs, group-oriented therapy, and individual behavioral therapy. Although cognitive function training for patients with AUD has recently gained increasing attention,[39] such interventions may be helpful only for patients at a relatively early stage of AUD who still possess the possibility of reversible recovery in cognitive functioning. More supportive treatments, including environmental rearrangements, may be adequate for older patients with AUD and progressive cognitive decline.

Despite providing important insights into the cognitive impact of AUD on the clinical course, our study had several limitations that need to be addressed in future research. First, the study was conducted on a modest number of Japanese patients, suggesting a potential regional influence. Accordingly, the present findings need to be generalized to broader and more diverse populations. Second, the BACS was originally developed to assess cognitive function in patients with schizophrenia. The validity of its application to patients with AUD is a significant consideration. Furthermore, the suitability of the timing for cognitive assessments (4 week post-abstinence) may need to be reconsidered. Although patterns of cognitive impairment may not greatly differ among psychiatric disorders,[33] the timing of cognitive assessments varies among studies for patients with AUD[40] and is still an issue to be debated. Third, whether irreversible cognitive decline exists or potential plasticity still remains in patients with AUD over the critical age (≥50 years) should be determined. Further investigations are needed to determine which specific brain regions are affected by alcohol intake, including the relationship with the dominant hemisphere and detailed brain functions.

AUTHOR CONTRIBUTIONS

Kazuhiro Kurihara, Ayano Shiroma, Munenaga Koda, Hotaka Shinzato, Yoshikazu Takaesu, and Tsuyoshi Kondo designed the study, wrote the protocol, performed the statistical analyses, and wrote the manuscript. Kazuhiro Kurihara and Tsuyoshi Kondo collected the data and verified the manuscript. Tsuyoshi Kondo raised the funding sources. All authors contributed to the manuscript and approved this submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data of the present study were not made publicly available because of the fact that the disclosure of individual data was not included in the research protocol and consent for public data sharing was not obtained from the participants.

ETHICS STATEMENT

Approval of the Research Protocol by an Institutional Reviewer Board: The study protocol was approved by the Ethics Committee of the National Hospital Organization Ryukyu Hospital, Approval No. 29–21.

Informed Consent: All the participants provided written informed consent before participating in the study.
Registry and the Registration No. of the Study/trial: N/A.
Animal Studies: N/A.

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REFERENCES

1. Wiegmann C, Mick I, Brandl EJ, Heinz A, Gutwinski S. Alcohol and dementia – what is the link? A systematic review. Neuropsychiatr Dis Treat. 2020;16:87–99.
2. Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. Alcohol Alcohol Suppl. 2000;35(1):2–7.
3. Sachdeva A, Chandra M, Choudhary M, Dayal P, Anand KS. Alcohol-related dementia and neurocognitive impairment: a review study. Int J High Risk Behav Addict. 2016;5(3):e27976.
4. Schwarzinger M, Pollock BG, Hasan OSM, Dufouil C, Rehm J, Study GQ. Contribution of alcohol use disorders to the burden of dementia in France 2008–13: a nationwide retrospective cohort study. Lancet Public Heal. 2018;3(3):e124–32.
5. Sullivan EV, Pfefferbaum A. Brain-behavior relations and effects of aging and common comorbidities in alcohol use disorder: a review. Neuropsychology. 2019;33(6):760–80.
6. Rao R, Topiwala A. Alcohol use disorders and the brain. Addiction. 2020;115(8):1580–9.
7. Ballard C, Lang I. Alcohol and dementia: a complex relationship with potential for dementia prevention. Lancet Public Heal. 2018;3(3):e103–4. https://doi.org/10.1016/S2468-2667(18)30031-8
8. Le Berre AP, Fama R, Sullivan EV. Executive functions, memory, and social cognitive deficits and recovery in chronic alcoholism: a critical review to inform future research. Alcohol Clin Exp Res. 2017;41(8):1432–43.
9. Khemiri L, Brynte C, Stunkel A, Klingberg T, Jayaram-Lindström N. Working memory training in alcohol use disorder: a randomized controlled trial. Alcohol Clin Exp Res. 2019;43(1):135–46.
10. Lahbairi N, Laniepce A, Segobin S, Cabé N, Boudehent C, Vabret F. Determinants of health-related quality of life in recently detoxified patients with severe alcohol use disorder. Health Qual Life Outcomes. 2022;20(1):149.
11. Nowakowska-domaga K, Jab K, Mokros Ł, Koprowicz J, Pietras T. Differences in the verbal fluency, working memory and executive functions in alcoholics: short-term vs. long-term abstainers. Psychiatry Res. 2017;249:1–8.
12. Maharjan S, Amjad Z, Abaza A, Vasavada AM, Sadhu A, Valencia C, et al. Executive dysfunction in patients with alcohol use disorder: a systematic review. Cureus. 2022;14(9):e29207.
13. Martín-González C, Godoy-Reyes AM, Abreu-González P, Fernández-Rodríguez CM, Martín-Ponce E, Sánchez-Pérez MJ, et al. Sclerostin, vascular risk factors, and brain atrophy in excessive drinkers. Front Hum Neurosci. 2023;21(17):1084756.
14. Moorman DE. The role of the orbitofrontal cortex in alcohol use, abuse, and dependence. Prog Neuropsychopharmacol Biol Psychiatry. 2018;87(Pt A):85–107.
15. Beylergil SB, Beck A, Deserno L, Lorenz RC, Rapp MA, Schlagenhauf F, et al. Dorsolateral prefrontal cortex contributes to the impaired behavioral adaptation in alcohol dependence. NeuroImage Clin. 2017;15:80–94.
16. Finn PR, Justus A, Mazas C, Steinmetz JE. Working memory, executive processes and the effects of alcohol on go/No- go learning: testing a model of behavioral regulation and impulsivity. Psychopharmacol. 1999;146(4):465–72.
17. Hagen E, Erga AH, Hagen KP, Nesvåg SM, Mckay JR, Lundervold AJ, et al. Journal of substance abuse treatment one-year sobriety improves satisfaction with life, executive functions and psychological distress among patients with polysubstance use disorder. J Subst Abuse Treat. 2017;76:81–7. https://doi.org/10.1016/j.jsat.2017.01.016
18. Loeber S, Duka TT, Welzel H, Nakovics H, Heinz A, Flor H, et al. Impairment of cognitive abilities and decision making after chronic use of alcohol: the impact of multiple detoxifications. Alcohol Alcohol. 2009;44(4):372–81.
19. Houck JM, Feldstein Ewing SW. Working memory capacity and addiction treatment outcomes in adolescents. Am J Drug Alcohol Abuse. 2018;44(2):185–92.
20. Bruijnen C, Walvoort S, Dijkstra B, de Jong C, Kessels R. The course of cognitive performance during inpatient treatment in patients with alcohol use disorder with no, mild or major neurocognitive disorders. Alcohol Alcohol. 2021;56(1):89–100.
21. Caballeria E, Oliveras C, Nunõ L, Balcells-Oliveró M, Gual A, López-Pelayo H. A systematic review of treatments for alcohol-related cognitive impairment: lessons from the past and gaps for future interventions. Psychol Med. 2020;50(13):2113–27.
22. Copersino ML, Fals-Stewart W, Fitzmaurice G, Schretlen DJ, Sokoloff J, Weiss RD. Rapid cognitive screening of patients with substance use disorders. Exp Clin Psychopharmacol. 2009;17(5):337–44.
23. Nixon SJ, Lewis B. Cognitive training as a component of treatment of alcohol use disorder: a review. Neuropsychology. 2019;33(6):822–41.
24. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The brief assessment of cognition in schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr Res. 2004;68(2–3):283–97.
25. Kaneda Y, Sumiyoshi T, Keefe R, Ishimoto Y, Numata S, Ohmori T. Brief assessment of cognition in schizophrenia: validation of the Japanese version. Psychiatry Clin Neurosci. 2007;61(6):602–9.
26. Kaneda Y, Sumiyoshi T, Nakagome K, Ikezawa S, Ohmori T, Yasui-furukori N, et al. Evaluation of cognitive functions in a Normal population in Japan using the brief assessment of cognition in schizophrenia Japanese version (BACS-J). Clin Psychiatry. 2013;55(2):167–75.
27. Keefe RSE, Fox KH, Davis VG, Kennel C, Walker TM, Burdick KE, et al. The brief assessment of cognition in affective disorders (BAC-A):performance of patients with bipolar depression and healthy controls. J Affect Disord [Internet]. 2014;166:86–92. https://doi.org/10.1016/j.jad.2014.05.002
28. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013.
29. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.
30. Saunders JB, Aasland OG, Babor TF, De La Fuente JR, Grant M. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction. 1993;88(6):791–804.
31. Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, et al. The 16-item quick inventory of depressive symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. Biol Psychiatry. 2003;54(5):573–83.
32. Yoneatsu O, Sachio M, Tomonobu S, Hisanori H, Higuchi S. Nationwide survey of alcohol drinking and alcoholism among Japanese adults. Nihon Arukoru Yakubutsu Igakkai Zasshi. 2005;40(5):455–70.

33. Ministry of Health L, Welfare. National Health and nutrition survey | Ministry of Health. Labour and Welfare. 2018 Available from: http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/kenkou/kenkounippon21/en/eiyouchousa/
34. Terachi S, Yamada T, Pu S, Yokoyama K, Matsumura H, Kaneko K. Comparison of neurocognitive function in major depressive disorder, bipolar disorder, and schizophrenia in later life: a cross-sectional study of euthymic or remitted, non-demented patients using the Japanese version of the brief assessment of cognition i. Psychiatry Res. 2017;254:205–10. https://doi.org/10.1016/j.psychres.2017.04.058
35. Bøstrand SMK, Harris MA, Cole JH, Cox SR, Marioni RE, Mccartney DL, et al. Associations between alcohol use and accelerated biological ageing. Addict Biol. 2022;27(1):e13100.
36. Chen H, Liang L, Xu H, Xu J, Yao L, Li Y, et al. Short term exposure to bilirubin induces encephalopathy similar to Alzheimer's disease in late life. J Alzheimers Dis. 2020;73(1):277–95.
37. Rosselli M, Uribe IV, Ahne E, Shihadeh L. Culture, ethnicity, and level of education in Alzheimer's disease. Neurotherapeutics. 2022;19(1):26–54. https://doi.org/10.1007/s13311-022-01193-z
38. Abdul Ghani AM, Faiz E, Nielsen A, Bilberg R. What is the cause of death, when alcohol dependent persons die prematurely? Drug Alcohol Depend. 2019;197:120–6. https://doi.org/10.1016/j.drugalcdep.2018.11.032
39. Bickel WK, Moody L, Quisenberry A. Computerized working-memory training as a candidate adjunctive treatment for addiction. Alcohol Res Curr Rev. 2014;36(1):123–6.
40. Fein G, McGillivray S. Cognitive performance in long-term abstinent alcoholics. Alcohol Clin Exp Res. 2006;30(9):1538–44.

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