ORIGINAL

Key Biomarkers and Physical Performance Indicators Associated with Pre-Frailty and Frailty in Patients with Chronic Schizophrenia aged <65 years

Toshiya Akiyama[1], Ryuichi Tanioka[2], Hirokazu Ito[3], Krishan Soriano[4,5], Leah Anne Bollos[5], Allan Paulo Blaquera[4], Kyoko Osaka[6], Hidehiro Umehara[7], Reiko Kamoi[8], Yoshihiro Mifune[8], Rick Yiu Cho Kwan[9], Anson Chui Yan Tang[9], Kazushi Mifune[8], and Tetsuya Tanioka[3]

[1]Department of Nursing, Kawasaki University of Medical Welfare, Okayama, Japan, [2]Faculty of Health Sciences, Hiroshima Cosmopolitan University, Hiroshima, Japan, [3]Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan, [4]Graduate School, St. Paul University Philippines, Tuguegarao City, Cagayan 3500, Philippines, [5]Graduate School of Health Sciences, Tokushima University, Tokushima, Japan, [6]Department of Nursing, Nursing Course of Kochi Medical School, Kochi University, Kochi, Japan, [7]Health Service, Counseling and Accessibility Center, Tokushima University, Tokushima, Japan, [8]Mifune Hospital, Kagawa, Japan, [9]School of Nursing, Tung Wah College, Hong Kong, China

Abstract : Patients with schizophrenia have a higher risk of early death, an average life expectancy 10-25 years lesser, and higher risk of frailty than the general population. This study aimed to determine the relationship between A Body Shape Index (ABSI), body mass index (BMI), chlorpromazine (CP) equivalent dose, and blood urea nitrogen to creatinine (BUN/Cr) ratio in hospitalized patients with chronic schizophrenia, with pre-frailty/frailty, and age <65 years. The Shapiro-Wilk test was used to analyze normality. Non-parametric methods were used for analysis. The study included 67 of 175 patients with chronic schizophrenia who were hospitalized and eligible for inclusion. Sixty-one patients were diagnosed with pre-frailty or frailty. Among the participants, 68.9% were pre-frailty, 31.1% were frailty, and 63.9% were at high mortality risk. Walking speed was significantly less in patients with frailty, highlighting its role in frailty assessment. The ABSI z-score was negatively correlated with grip strength, thereby linking abdominal obesity to muscle weakness. The BUN/Cr ratio was also correlated with grip strength, walking speed, and BMI, suggesting metabolic influences on frailty. Frailty in patients with schizophrenia often occurs at a younger age in patients with schizophrenia than in the general population, and routine assessment of ABSI z-score and BUN/Cr levels could offer valuable prognostic information. J. Med. Invest. 73 : 12-20, February, 2026

Keywords **:** *frailty, pre-frailty, schizophrenia, mortality risk, ABSI z-score*

INTRODUCTION

Schizophrenia is a chronic mental illness affecting approximately 1% of the global population (1), with most patients in the age group of 25-54 years (2). In addition to significant psychosocial challenges, individuals with schizophrenia are at increased risk of metabolic and physical complications, including insulin resistance, cardiovascular disease, and poor nutrition (3-5). These comorbidities contribute to a shortened life expectancy of 10-25 years (6). Frailty, defined as a "multisystem decline in the physiologic ability to endure minor environmental stresses (7)," is often associated with these conditions. Individuals with schizophrenia are particularly vulnerable to early-onset frailty (8), which is linked to deteriorating physical health, increased mortality, and reduced quality of life (9). Nonetheless, data on frailty in adults with schizophrenia aged <65 years are limited (10), particularly in long-term care settings.

Frailty develops bceause of an interplay of systemic inflammation, oxidative stress, metabolic dysfunction, hormonal dysregulation, and musculoskeletal decline (11). Frailty leads to various health conditions, such as limitations in activities of daily living, increased incidence of falls, low quality of life, sleep disturbances, slow mobility, hearing impairment, and a decline in cognitive status, nutritional status, functional ability, and quality of physical health (12, 13). Insulin resistance and obesity are known contributors, as they promote metabolic dysfunction, leading to chronic inflammation, muscle wasting, and impaired strength (14-16). Cardiovascular disease, a leading cause of death in patients with schizophrenia (3), shares common pathophysiological pathways with frailty, including oxidative stress and endothelial dysfunction. Similarly, malnutrition and chronic inflammation further degrade physical health, increasing vulnerability to frailty (10). These overlapping mechanisms should be assessed in high-risk groups for frailty.

Several assessment tools have been developed over recent decades for the prompt identification of frailty. One of the most

Abbreviations
The following abbreviations are used in this manuscript :
BUN/Cr ratio, Blood urea nitrogen to creatinine ratio ; BMI, Body mass index ; WC, Waist circumference ; ABSI, A Body Shape Index ; CP, Chlorpromazine ; DSM-5, Fifth edition of Diagnostic and Statistical Manual of Mental Disorders ; BUN, Blood urea nitrogen ; Cr, Creatinine ; CHS, Cardiovascular Health Study ; Revised J-CHS criteria, Revised Japanese version of the Cardiovascular Health Study criteria

Received for publication April 21, 2025 ; accepted July 25, 2025.

Address correspondence and reprint requests to Toshiya Akiyama, Department of Nursing, Kawasaki University of Medical Welfare, Okayama 701-0193, Japan and E-mail : aki.5.toshi.2@gmail.com

widely recognized and established methods is the physical frailty phenotype, as described by Fried *et al*. (17). The potential of serum biomarkers for inflammation (11) and general laboratory indices, such as blood urea nitrogen to creatinine (BUN/Cr) ratio, has been documented (18). The BUN/Cr ratio is a valuable tool for evaluating frailty-related risks, particularly in older populations (19-21). These markers offer insights into protein metabolism, renal function, and nutritional status, and are therefore relevant for frailty assessment in psychiatric patients. Elevated BUN levels (19, 20) are strongly associated with higher in-hospital mortality, even after adjusting for kidney dysfunction. Because frail individuals frequently exhibit metabolic alterations and muscle wasting, BUN/Cr variability may reflect accelerated catabolism in patients with schizophrenia, particularly those with progressive physical impairment. Since BUN is a byproduct of protein metabolism, its elevation may indicate reduced renal clearance and increased muscle degradation, which are frequently observed in frailty.

Physical frailty and sarcopenia show extensive clinical similarities (22). In particular, BUN/Cr ratio and the risk of sarcopenia are associated with the skeletal muscle area index (23) and grip strength (24). These findings suggest that BUN/Cr ratio may serve as a useful screening index for physical frailty (25).

Both general obesity, characterized by a high Body Mass Index (BMI), and abdominal obesity, defined by an increased Waist Circumference (WC), elevate the risk of frailty in older individuals (26). Recently, the A Body Shape Index (ABSI) z-score, derived from ABSI, which evaluates health impacts based on body shape (height, weight, and WC), has gained attention as a superior mortality risk indicator associated with obesity compared with BMI (27). ABSI is also correlated with mortality as a result of diabetes, metabolic syndrome, and cardiovascular disease (28, 29). Furthermore, low grip strength, high ABSI z-score, and increased mortality risk have been previously correlated (30).

Metabolic syndrome further increases the risk of physical inactivity in patients with schizophrenia (31). The mortality risk may also be influenced by the side effects of antipsychotic drugs because antipsychotic medications cause movement disorders, sedation, and weight gain, which are associated with sudden death (32).

Clinically significant weight changes often occur as side effects of antipsychotic drugs (33). However, the underlying mechanism is unknown (34).

Hence, it is critical to determine the relationship between antipsychotic medication use and WC, ABSI z-score, and BMI. However, no previous study has examined these relationships.

ABSI is a more reliable predictor of frailty than BMI (35) ; however, few studies have explored its relationship with physical frailty in adult patients with schizophrenia. Individuals with schizophrenia often face nutritional challenges due to inadequate self-care, lack of food preparation skills, and unhealthy lifestyle. Despite this, nutritional deficiencies in this population are frequently overlooked, though chronic conditions, including mental health disorders, can severely impact the quality of life (36, 37). Growing evidence suggests that improved nutrition may support mental well-being and aid in managing psychiatric disorders (38).

This study aimed to determine the relationship among ABSI, BMI, chlorpromazine (CP) equivalent doses, and BUN/Cr ratio in hospitalized patients having chronic schizophrenia with pre-frailty and frailty and aged <65 years. Specifically, we sought to answer three research questions to address the main research objective.

1. What is the ABSI z-score-based mortality risk among patients with pre-frailty and frailty having chronic schizophrenia?
2. Is there a significant difference in the ABSI z-score, BMI, CP equivalent doses, walking speed, grip strength, and BUN/Cr ratio between patients with pre-frailty and frailty having chronic schizophrenia?
3. Are there significant paired relationships among ABSI z-score, BMI, CP equivalent doses, walking speed, grip strength, and BUN/Cr ratio in hospitalized patients with pre-frailty and frailty, aged <65 years, and having chronic schizophrenia?
4. What is the relationship between obesity and atypical antipsychotic use?

MATERIALS AND METHODS

Study Design

This observational, cross-sectional study was reported using the Strengthening the Reporting of Observational Studies in Epidemiology checklist (39). Data were collected between May 18 and December 28, 2024.

Setting

The study was set in Mifune Hospital in Japan, which was founded in 1953, and is a 328-bed psychiatric hospital. It has departments of psychiatry, internal medicine, dentistry, and oral surgery.

Participants

Participants who fulfilled the following eligibility criteria were recruited for this study. Of the 175 patients with chronic schizophrenia, 67 were hospitalized and eligible for study inclusion. However, 102 patients were excluded from the analysis due to severe mental symptoms, such as delusions, which prevented them from undergoing a frailty assessment or having their waist circumference measured (N = 98) or blood drawn (N = 92).

Of the 67 patients, 61 patients (31 male, 30 female) were diagnosed with pre-frailty or frailty. Six subjects were excluded from the analysis because they were not evaluated as frailty.

Inclusion Criteria

Schizophrenia is associated with an increased risk of mortality and physical comorbidities, which suggests that the frailty process may be accelerated in affected individuals (40). However, the prevalence and prognostic influence of frailty status in adults with schizophrenia are not well understood (41). This study focused on inpatients diagnosed with schizophrenia according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and ranging in age from 20 to 64.

Exclusion Criteria

The exclusion criteria were designed to ensure participant safety and to maintain the focus of the study on pre-frailty and frailty.

1. Participants with severe mental disorders other than schizophrenia, as defined by the DSM-5 criteria (delusional, bipolar and related, depressive, neurodevelopmental, substance-related and addictive, or personality disorders).

2. Participants with co-existing conditions that would prevent full participation in the study (cerebrovascular disease, stroke or other neurological diseases, cancer, dehydration, reduced blood flow to the kidneys, congestive heart failure, gastrointestinal bleeding, urinary tract obstruction, acute kidney injury, or chronic kidney disease).

3. Participants with pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy defibrillators.

Measurements

Demographics

Data pertaining to age and sex were retrieved from the participants' medical records.

ABSI z-scores

The standardized value of the ABSI z-score [WC/(BMI 2/3 *m 1/2)], an index of abdominal obesity independent of BMI, is a strong predictor of frailty (35).

Cox proportional hazard modeling for assessing mortality risk was used with ABSI z-score quintiles considered as predictors. Hazard ratios are relative to the middle quintile. The ranges in parentheses are 95% confidence intervals. The ABSI z-score allows classification of patients into health risk groups. The between-quintile cutoff points for ABSI z-scores are as follows : <0.868, very low ; between 0.868 and 0.272, low ; between -0.272 and +0.229, average ; between +0.229 and +0.798, high ; and >+0.798, very high risk (30).

There is no consensus on the optimal anatomical position for WC measurement. Measurement around the navel is less accurate than measurement at the midpoint between the last palpable rib and the iliac crest, but is more convenient for large-scale health screening (42, 43). In addition, approximately one third of patients with schizophrenia and frailty have a BMI >30 kg/m^2 (44). Palpating the bones is difficult in such patients. Therefore, we measured WC at the umbilical circumference.

Frail patients have significantly higher WC, body fat mass, and body fat percentage than non-frail patients and non-frail patients have significantly higher skeletal muscle mass and total body water than frail patients. Individuals with a normal BMI but a large WC, measured at the abdominal circumference, are at a high risk of frailty (45, 46).

BMI

BMI is calculated using a person's height in meters and weight in kilograms using the following formula : BMI = kg/m^2.

CP Equivalent Doses

The types and doses of atypical antipsychotics were also recorded. The types of medications included olanzapine, risperidone, aripiprazole, ziprasidone, clozapine, amisulpride, quetiapine fumarate, and paliperidone extended-release tablets. The daily doses of the prescribed antipsychotic drugs were converted to the equivalent daily dose of CP per 100 mg, based on the international consensus (47, 48).

The recommended daily limit for CP equivalents is 400 mg (49) or 600 mg per day (50). However, a dosage above 1,000 mg of CP equivalents per day is considered high (51). Thus, CP equivalents were classified into three groups : Group 1 : CP <400 ; Group 2 : CP >400 ; and Group 3 : CP >1,000.

BUN/Cr Ratio

The BUN/Cr ratio is an indicator of muscle wasting, and since a BUN/Cr ratio ≥10 is associated with the prognosis of frailty, we considered BUN/Cr ratio ≥10 as abnormal (24).

Walking Speed

Using a gait analysis system (manufactured by NEC), we measured the walking speed of patients walking at a normal pace over a distance of approximately 6 meters.

Grip Strength

Muscle strength was measured by using a digital grip dynamometer (T. K. K. 5401 ; Takei Scientific Instruments, Co., Ltd., Niigata, Japan). Grip strength was used as an indicator of muscle weakness, the cutoff for which was defined for men and women at a grip strength of 26 and 18 kg, respectively. The mean grip strength was calculated for each hand.

Physical Frailty and Mortality Risk :

The revised Japanese version of the Cardiovascular Health Study criteria (revised J-CHS criteria) is used to assess frailty based on the presence of three or more out of five assessment items (unintentional weight loss, muscle weakness, exhaustion, walking speed, and physical activity) (17, 52, 53). Objective data were determined by weight loss (2-3 kg weight loss in 6 months), muscle weakness (grip strength <26 kg for men and <18 kg for women), and walking speed (normal walking speed of less than 1.0 m/s). For the walking speed assessment, a space was prepared for walking 11 m in a straight line (5 m measurement walkway and 3 m auxiliary walkways in front and behind), and the walking speed over 5 m was measured (54).

Statistical Method

The variables were first described based on their measurement levels. The Shapiro–Wilk test was used to analyze normality. Owing to the small sample size, non-parametric methods were used to describe the variables (i.e., frequencies with percentages for categorical variables and medians with minimum to maximum values for continuous variables). The following methods were used to answer research questions 1-4 : 1) Cross tabulation ; 2) Mann-Whitney U test ; 3) Spearman's correlation coefficient ; and 4) Kruskal-Wallis test with Dwass-Steel-Critchlow-Fligner pairwise comparisons.

All statistical analyses were performed using the Jamovi Statistical Software Version 2.4.11.0 (55). For all analyses, statistical significance was defined as $p<0.05$.

Sample Size Calculation

The sample size was calculated using the G*Power software (ver. 3.1.9.7;) (56). Assuming a one-way analysis of variance between the three groups with an effect size of 0.42, alpha level of 0.05, and power of 0.80, the required sample size was calculated as 60.

RESULTS

Descriptive Data

There were 67 eligible participants. Of these, only 61 patients completed all the tests. The descriptive data for all variables are presented in Table 1. The median (minimum-maximum) age of the participants was 52 (21-65) years. Figure 1 provides detailed information on age distribution of patients. The study sample was evenly distributed with 31 males (50.8%) and 30 females (49.2%). Participants had a median height of 162 (144-178) cm, weight of 63.9 (45-110) kg, WC of 90 (65-118) cm, ABSI z-score of 0.8 (-3.7-4.9), BMI of 24.6 (17-34.7) kg/m^2, and CP equivalent doses of 750 (75-2382) mg/day.

Mortality risk classification showed that, according to the ABSI z-score, 50.8% patients were at a very high risk.

For the evaluation items in the revised J-CHS criteria, 19.7% of patients responded that they felt tired, and 57.4% responded that they did not perform any physical activity. The median handgrip strength was 19.3 kg (left) and 20.8 kg (right), and the walking speed was 0.9 m/s. As a result, 31.1% patients were evaluated as frailty and 68.9% as pre-frailty. The median BUN level was 10.9 mg/dL, and the BUN/Cr ratio was 16.

As shown in Table 2, 50.8% of patients had a "very high" mortality risk, 13.1% had a "high" mortality risk, and a total of 63.9% had a high mortality risk, representing the majority.

Table 3 shows the variables compared between the pre-frail and frail groups. Walking speed was significantly less in the frail group (0.71 m/s [0.25-1.28]) than in the pre-frail group (0.95 m/s [0.28-1.28]) (p<.001). However, no significant differences were observed in the other variables.

As shown in Table 4, the correlation between the ABSI z-score, CP equivalent dose, walking speed, mean grip strength, BUN/Cr ratio, and BMI was evaluated. CP equivalent doses were not significantly correlated with ABSI z-score and other indicators. Significant relationships were found between the ABSI z-score and mean grip strength (ρ= -0.4, $p < .01$) and between mean grip strength and BUN/Cr ratio (ρ= -0.39, $p < .01$). Walking speed was positively correlated with BUN/Cr ratio (ρ= 0.27, $p < .05$). BMI was negatively correlated with BUN/Cr ratio (ρ= -0.45, $p < .001$).

Table 5 shows the evaluation of the relationship between obesity indicators (BMI, WC, ABSI, and ABSI Z-score) and atypical antipsychotics. However, no significant relationship was found.

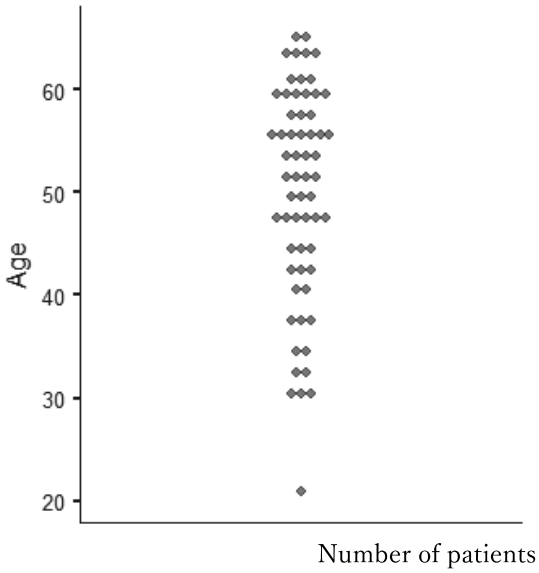

Figure 1. Detailed age distribution of patients

Table 1. Descriptive data for all variables (N = 61)

Variables	Median (minimum-maximum)/ Frequency (%)
Demographics	
Age, years	52 (21-65)
Sex	
Male	31 (50.8%)
Female	30 (49.2%)
Body composition	
Height, cm	162 (144-178)
Weight, kg	63.9 (45-110)
Waist circumference (cm)	90 (65-118)
ABSI z-score	0.8 (-3.7-4.9)
Body mass index, kg/m^2	24.6 (17-34.7)
Chlorpromazine equivalent dose, mg/day	750 (75-2382)
Mortality risk by ABSI z-score	
Very low	6 (9.8%)
Low	7 (11.5%)
Average	9 (14.8%)
High	8 (13.1%)
Very high	31 (50.8%)
Revised Japanese version of the Cardiovascular Health Study criteria	
Feeling tired	19.7 (%)
Not doing physical activity	57.4 (%)
Hand grip strength	
Left, kg	19.3 (6-41)
Right, kg	20.8 (11.1-46.4)
Walking speed, m/s	0.9 (0.3-1.3)
Frequencies of occurrence of pre-frailty/frailty	
Pre-frailty	42 (68.9%)
Frailty	19 (31.1%)
Blood parameters	
BUN, mg/dL	10.9 (5.3-34.7)
Cr, mg/dL	0.7 (0.4-1.9)
BUN/Cr ratio	16 (7.3-29.8)

ABSI, A Body Shape Index ; BUN, blood urea nitrogen ; Cr, creatinine

DISCUSSION

Walking speed was significantly less in patients with frailty, highlighting its role in frailty assessment. The ABSI z-score was negatively correlated with grip strength, thereby linking abdominal obesity to muscle weakness. The BUN/Cr ratio was also correlated with grip strength, walking speed, and BMI, suggesting that metabolism influences frailty.

The study sample consisted of participants with a balanced sex distribution and a median age of 52 year. Pre-frailty was prevalent in 68.9% of participants, whereas frailty in 31.1%, reflecting early-onset frailty in this population. This high prevalence of pre-frailty suggests that a subtle physiological decline may begin earlier in patients with schizophrenia than in the general population, warranting proactive monitoring and intervention (8).

Based on the ABSI z-score-based mortality index, 63.9% of participants had "high" or "very high" risk of mortality, emphasizing the prognostic value of this index in predicting adverse outcomes. These findings are consistent with prior research demonstrating the association between frailty, abdominal obesity, and mortality risk, particularly in populations with chronic

Table 2. Cross-tabulation of pre-frailty, frailty, and mortality risk according to A Body Shape Index z-score

Pre-frailty or frailty		Mortality risk by ABSI z-score					Total
		Very low	Low	Average	High	Very high	
Pre-frailty	Observed	5	5	7	5	20	42
	% of total	8.2%	8.2%	11.5%	8.2%	32.8%	68.9%
Frailty	Observed	1	2	2	3	11	19
	% of total	1.6%	3.3%	3.3%	4.9%	18.0%	31.1%
Total	Observed	6	7	9	8	31	61
	% of total	9.8%	11.5%	14.8%	13.1%	50.8%	100.0%

Table 3. Comparison of variables between groups : pre-frail vs. frail

	Pre-frail (N = 42) Median (minimum-maximum)	Frail (N = 19) Median (minimum-maximum)	Statistics p-value
Age, years	53.0 (30-65)	50.5 (21-65)	0.4
A Body Shape Index z-score	0.8 (-3.7-4.9)	1.0 (-1.2-4.1)	0.7
Body mass index, kg/m^2	25.3 (17-34.7)	24.6 (17-32.4)	0.8
Chlorpromazine equivalent dose, mg/day	700 (75-2382)	879 (125-1881)	0.1
Walking speed, m/s	0.95 (0.28-1.28)	0.71 (0.25-1.28)	<.001
Mean grip strength, kg	20.6 (11.5-42.1)	19.0 (9-39.1)	0.2
BUN, mg/dL	11.0 (5.3-34.7)	10.7 (6.7-25.6)	0.3
Cr, mg/dL	0.7 (0.4-1.9)	0.7 (0.5-1.1)	0.9
BUN/Cr ratio, mg/dL	16 (7.3-22)	16.8 (8.4-29.8)	0.3

Mann-Whitney U test, BUN, blood urea nitrogen ; Cr, creatinine

Table 4. Correlation matrix for ABSI z-score, WC, BMI, CP equivalent dose, walking speed, mean grip strength, and BUN/Cr ratio

	ABSI z-score	WC	BMI	CP equivalent dose	Walking speed	Mean grip strength
WC, cm	0.5 ***	—				
BMI, kg/m^2	0.01	0.81 ***	—			
CP dose, mg/day	-0.01	0.12	0.14	—		
Walking speed, m/s	-0.002	-0.16	-0.18	-0.05	—	
Mean grip strength, kg	-0.4 **	-0.02	0.11	-0.16	-0.07	—
BUN/Cr ratio	0.03	-0.34 **	-0.45 ***	0.1	0.27 *	-0.39 **

ABSI, A Body Shape Index ; WC, waist circumference ; BMI, body mass index ; CP, chlorpromazine ; BUN, blood urea nitrogen ; Cr, creatinine ; *p < .05, **p < .01, ***p < .001

Table 5. Relationship between chlorpromazine equivalent doses and obesity

	Counts	% of Total	Cumulative %
CP <400 (1)	16	26.2%	26.2%
CP >400 (2)	33	54.1%	80.3%
CP >1000 (3)	12	19.7%	100.0%
	χ^2	df	p
Body Mass Index	1.2	2	0.6
Waist Circumference	2.0	2	0.4
A Body Shape Index	1.9	2	0.4
A Body Shape Index (Z score)	0.3	2	0.8

CP : chlorpromazine equivalent doses, Kruskal-Wallis test

illnesses (30).

Frailty is more likely to occur in middle-aged and older adults who are obese with visceral fat (57, 58). These findings highlight the prognostic value of the ABSI z-score in predicting outcomes (35). While previous studies have assessed frailty in the older population, this study revealed an association between frailty and visceral obesity and an increased risk of death in patients with schizophrenia aged 65 or younger.

The ABSI z-score is a superior predictor of mortality risk than BMI alone (27). The distribution of mortality risk underscores the vulnerability of patients with chronic schizophrenia to early physical health decline and mortality (6), which supports the use of the ABSI z-score as an objective tool for identifying patients who require close monitoring and targeted interventions (26).

No significant differences were observed in ABSI z-score, CP equivalent doses, BMI, grip strength, or BUN/Cr ratio between the pre-frail and frail groups. However, walking speed was significantly different between pre-frail and frail groups. This finding is consistent with a prior research suggesting that a slower walking speed is a hallmark indicator of frailty (17). Furthermore, handgrip strength is a clinically useful indicator of slow walking, which is detrimental to the health of older adults (59, 60). Functional performance metrics, such as handgrip strength and walking speed, were significantly impaired in participants with frailty, consistent with established frailty criteria (60, 61). Reduced muscle strength and slower walking speed reflect progressive neuromuscular decline, a hallmark of frailty that increases the risk of falls, disability, and loss of independence (60, 61). However, walking speed alone was not an effective measure of frailty, and other biomarkers should be considered to capture the multidimensional nature of frailty.

In determining the significant relationships among the variables, the inverse correlation of BUN/Cr ratio with grip strength and BMI suggests that metabolic alterations and increased catabolism may contribute to muscle weakness in frail individuals (24, 30). This is consistent with reports indicating that elevated BUN/Cr ratios reflect increased muscle breakdown and poor nutritional status (23), and body shape and central adiposity are linked to reduced muscle function (28).

The positive correlation between walking speed and BUN/Cr ratio may reflect the complex interplay between muscle function and metabolic processes (62). This may indicate that early-stage metabolic dysfunction is associated with a decline in physical performance before overt frailty becomes evident (18). Because frailty often appears at a younger age in patients with schizophrenia than in the general population, routine assessment of BUN/Cr ratio levels could offer valuable prognostic information. This approach may help guide early interventions to slow physical decline, reduce progression of frailty, and improve long-term outcomes.

Patients with chronic schizophrenia and a normal body weight have higher visceral fat levels than healthy controls (63). Patients with schizophrenia are more likely to have central obesity because of metabolic syndrome than the general population (64). This suggests that central obesity is an important factor in predicting cardiovascular outcomes and may represent a mortality risk factor (65).

However, CP equivalent doses did not significantly affect ABSI z-score, BMI, or WC. A previous study (66) has shown that age, BMI, and CP equivalent dosage are associated with gender differences in changes to body composition (e.g., body fat percentage, muscle mass, and body water content) related to schizophrenia. Future studies should be tailored according to gender.

BMI and WC can be misleading regarding the degree of obesity in individuals with a normal weight (63). Therefore, visceral obesity and muscle mass loss should be measured using bioelectrical impedance analysis, which can quantify body composition variables.

These findings underscore the need for tailored interventions, including nutritional management, physical rehabilitation, and routine frailty screening using BUN/Cr ratio, ABSI z-scores, and J-CHS frailty index. Implementing these strategies may help mitigate frailty progression and improve overall health outcomes in this vulnerable population.

LIMITATIONS AND FUTURE STUDY

Some patients with schizophrenia had difficulty completing questionnaires all five items of the revised J-CHS criteria (weight loss, muscle weakness, fatigue, walking speed, and physical activity). If patients do not cooperate in the assessment, frailty cannot be assessed. Given the small sample size in this study, which may have led to false-negative results, a larger population is needed to further identify the associated risk factors. Future research with larger cohorts is needed to determine the relationship between CP equivalent doses, ABSI z-score, BMI, and WC, including visceral fat.

This study focused on patients aged 65 years or younger. Therefore, we did not compare their data with those of older patients. Future studies will compare the following groups : younger patients (aged 40 years or younger), middle-aged patients (aged 65 years or younger), and older patients (aged 65 years or older).

CONCLUSIONS

This study aimed to determine the relationship among ABSI z-score, BMI, CP equivalent dose, and BUN/Cr ratio in hospitalized patients with chronic schizophrenia and with pre-frailty and frailty aged <65 years. the following conclusions were drawn : 1) Concerningly, 63.9% of participants were categorized of having a "high" or "very high" risk of mortality based on the ABSI z-score, emphasizing the prognostic value of this index in predicting adverse outcomes. 2) The high prevalence of pre-frailty suggests that subtle physiological decline may begin earlier in patients with schizophrenia than in the general population, warranting proactive monitoring and intervention. 3) BUN/Cr variability may indicate increased catabolism in patients with schizophrenia, suggesting a role in frailty-related muscle wasting. 4) Frailty in patients with chronic schizophrenia appears to affect younger participants to a greater extent than in the general population. However, the CP equivalent dose was not significantly correlated with the ABSI z-score or other indicators.

The findings highlight the importance of monitoring the ABSI z-score, performing WC measurements, and assessing the BUN/Cr ratio and BMI to detect frailty and malnutrition. This approach may help guide early interventions to slow physical decline, reduce progression of frailty, and improve long-term outcomes.

FUNDING

This research received no external funding.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, T.A., R.T., and T.T. ; methodology, R.T., H.I., and T.T. ; validation, R.Y.C.K., A.T. H.U., and Y.M. ; formal analysis, R.T., H.I., and T.T. ; investigation, R.K., T.A, K.O., R.T., and T.T. ; writing—original draft preparation, T.A., K.O., R.T., H.I., and T.T. ; writing—review and editing, K.S., L.B., and T.T. ; project administration, T.T. All authors have read and agreed to the published version of the manuscript.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Tokushima University Hospital (#4210 on 27 July 2022) and the Mifune Hospital Clinical Research Ethics Review Committee (#20240320 on 20 March 2024).

INFORMED CONSENT STATEMENT

Informed consent was obtained from all participants involved in the study.

DATA AVAILABILITY STATEMENT

Data presented in this study are available upon request from the corresponding author. The data are not publicly available because of privacy and ethical restrictions.

ACKNOWLEDGMENTS

The authors express gratitude and appreciation to the participants. The authors thank the Mifune Hospital for assistance during the conduct of the research.

REFERENCES

1. He Y, Tanaka A, Kishi T, Li Y, Matsunaga M, Tanihara S, Iwata N, Ota A : Recent findings on subjective well-being and physical, psychiatric, and social comorbidities in individuals with schizophrenia : A literature review. Neuropsychopharm Rep 42 : 430-436, 2022
2. Baba K, Guo W, Chen Y, Nosaka T, Kato T : Burden of schizophrenia among Japanese patients : a cross-sectional National Health and Wellness Survey. BMC Psychiatry 22 : 410, 2022
3. Ali S, Santomauro D, Ferrari AJ, Charlson F : Schizophrenia as a risk factor for cardiovascular and metabolic health outcomes : a comparative risk assessment. Epidemiol Psychiatr Sci 32 : e8, 2023
4. Solmi M, Veronese N, Beatrice B, Stella R, Paolo S, Davide G, Collantoni E, Pigato G, Favaro A, Stubbs B, Carvalho AF, Vacampfort D, Correll CU : Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness : a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 16 : 163-180, 2017
5. Riera-Molist N, Assens-Tauste M, Roura-Poch P, Guimerà-Gallent M, Santos-López JM, Serra-Millas M, Frau-Rosselló N, Gallego-Peña E, Foguet-Boreu Q : A Cardiovascular Risk Optimization Program in People With Schizophrenia : A Pilot Randomized Controlled Clinical Trial. Journal of Psychiatric Practice 29 : 456-468, 2023
6. Laursen TM, Munk-Olsen T, Vestergaard M : Life expectancy and cardiovascular mortality in persons with schizophrenia. Current Opinion in Psychiatry 25 : 83-88, 2012
7. Campbell AJ, Buchner DM : Unstable disability and the fluctuations of frailty. Age Ageing 26 : 315-318, 1997
8. Arnautovska U, Siskind D, Pearson E, Baker A, Reid N, Kwan WWL, Wang N, Gordon E, Hubbard R, Warren N : Comprehensive Geriatric Assessment for younger outpatients with severe mental illness : protocol for a feasibility study. BMJ Open 13 : e069518, 2023
9. Warren N, Leske S, Arnautovska U, Northwood K, Kisely S, Siskind D : Prevalence of frailty in severe mental illness : findings from the UK Biobank. BJPsych open 9 : e185, 2023
10. Spiers GF, Kunonga TP, Hall A, Beyer F, Boulton E, Parker S, Bower P, Craig D, Todd C, Hanratty B : Measuring frailty in younger populations : a rapid review of evidence. BMJ Open 11 : e047051, 2021
11. Perazza LR, Brown-Borg HM, Thompson LV : Physiological Systems in Promoting Frailty. In : Comprehensive Physiology, 1st ed. Prakash YS (ed.) Wiley, pp3575-3620, 2022
12. Ho LYW, Cheung DSK, Kwan RYC, Wong ASW, Lai CKY : Factors associated with frailty transition at different follow-up intervals : A scoping review. Geriatric Nursing 42 : 555-565, 2021
13. Cheung DSK, Kwan RYC, Wong ASW, Ho LYW, Chin KC, Liu JYW, Tse MMY, Lai CKY : Factors Associated With

Improving or Worsening the State of Frailty : A Secondary Data Analysis of a 5-Year Longitudinal Study. J of Nursing Scholarship 52 : 515-526, 2020
14. Chhetri JK, Zheng Z, Xu X, Ma C, Chan P : The prevalence and incidence of frailty in Pre-diabetic and diabetic community-dwelling older population : results from Beijing longitudinal study of aging II (BLSA-II). BMC Geriatr 17 : 47, 2017
15. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y : Obesity and inflammation : the linking mechanism and the complications. aoms 4 : 851-863, 2017
16. d'Avila JDC, Georges Moreira El Nabbout T, Georges Moreira El Nabbout H, Silva ADS, Barbosa Ramos AC, Fonseca ERD, Santana Carlos A, Siqueira RDA : Correlation between low handgrip strength and metabolic syndrome in older adults : a systematic review. Archives of Endocrinology and Metabolism 68 : e230026, 2024
17. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA : Frailty in Older Adults : Evidence for a Phenotype. The Journals of Gerontology Series A : Biological Sciences and Medical Sciences 56 : M146-M157, 2001
18. Hirashiki A, Shimizu A, Suzuki N, Nomoto K, Kokubo M, Hashimoto K, Sato K, Kondo I, Murohara T, Arai H : Composite Biomarkers for Assessing Frailty Status in Stable Older Adults With Cardiovascular Disease. Circ Rep 4 : 123-130, 2022
19. Akpinar E, Hosgün D, Doganay B, Gulhan M : M. Blood urea nitrogen/albumin ratio : Is it a new predictor for prognosis of community-acquired pneumonia?
20. Singh K, Singh S : Blood Urea Nitrogen/Albumin Ratio and Mortality Risk in Patients with COVID-19. Indian Journal of Critical Care Medicine 26 : 626-631, 2022
21. Küçükceran K, Ayrancı MK, Girişgin AS, Koçak S, Dündar ZD : The role of the BUN/albumin ratio in predicting mortality in COVID-19 patients in the emergency department. The American Journal of Emergency Medicine 48 : 33-37, 2021
22. Picca A, Coelho-Junior HJ, Calvani R, Marzetti E, Vetrano DL : Biomarkers shared by frailty and sarcopenia in older adults : A systematic review and meta-analysis. Ageing Research Reviews 73 : 101530, 2022
23. Gao H, Wang J, Zou X, Zhang K, Zhou J, Chen M : High blood urea nitrogen to creatinine ratio is associated with increased risk of sarcopenia in patients with chronic obstructive pulmonary disease. Experimental Gerontology 169 : 111960, 2022
24. Chen X, Chen Z, Zhou W, Wang Y, Su J, Zhou Q : Blood urea nitrogen to creatinine ratio is associated with physical frailty in older-aged Chinese : a cross-sectional study. Aging Clin Exp Res 35 : 581-589, 2023
25. Kamoi R, Mifune Y, Soriano K, Tanioka R, Yamanaka R, Ito H, Osaka K, Umehara H, Shimomoto R, Bollos LA, Kwan RYC, Endo I, Palijo SrS, Noguchi K, Mifune K, Tanioka T : Association Between Dynapenia/Sarcopenia, Extrapyramidal Symptoms, Negative Symptoms, Body Composition, and Nutritional Status in Patients with Chronic Schizophrenia. Healthcare 13 : 48, 2024
26. Yuan L, Chang M, Wang J : Abdominal obesity, body mass index and the risk of frailty in community-dwelling older adults : a systematic review and meta-analysis. Age and Ageing 50 : 1118-1128, 2021
27. Nunnari A, Di Girolamo FG, Teraž K, Fiotti N, Šimunič B, Mearelli F, Pišot R, Biolo G : The Abdominal Adiposity Index (A Body Shape Index) Predicts 10-Year All-Cause Mortality in Elderly Active Non-Obese Subjects. JCM 13 : 6155, 2024
28. Shi J, Chen Z, Zhang Y : Associations between body fat anthropometric indices and mortality among individuals with metabolic syndrome. Lipids Health Dis 23 : 306, 2024
29. Lu C-Y, Chen H-H, Chi K-H, Chen P-C : Obesity indices and the risk of total and cardiovascular mortality among people with diabetes : a long-term follow-up study in Taiwan. Cardiovasc Diabetol 22 : 345, 2023
30. Krakauer NY, Krakauer JC : Association of Body Shape Index (ABSI) with Hand Grip Strength. IJERPH 17 : 6797, 2020
31. Vancampfort D, Sweers K, Probst M, Maurissen K, Knapen J, Minguet P, De Hert M : Association of the metabolic syndrome with physical activity performance in patients with schizophrenia. Diabetes & Metabolism 37 : 318-323, 2011
32. Ceraso A, Lin JJ, Schneider-Thoma J, Siafis S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM, Leucht S : Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database of Systematic Reviews 2020, 2020
33. Curtis J, Teasdale SB, Morell R, Wadhwa P, Watkins A, Lederman O, O'Donnell C, Fibbins H, Ward PB : Implementation of a lifestyle and life-skills intervention to prevent weight-gain and cardiometabolic abnormalities in young people with first-episode psychosis as part of routine care : The Keeping the Body in Mind program. Early Intervention Psych 18 : 731-738, 2024
34. Pringsheim T, Kelly M, Urness D, Teehan M, Ismail Z, Gardner D : Physical Health and Drug Safety in Individuals with Schizophrenia. Can J Psychiatry 62 : 673-683, 2017
35. Shafran I, Krakauer NY, Krakauer JC, Goshen A, Gerber Y : The predictive ability of ABSI compared to BMI for mortality and frailty among older adults. Front Nutr 11 : 1305330, 2024
36. Kim SR, Kim JY, Kim HY, Nho J, Kim YH, Min S : Factors related to malnutrition in community-dwelling patients with schizophrenia. Perspect Psychiatr Care 55 : 415-423, 2019
37. Sorić T, Mavar M, Rumbak I : Metabolic Syndrome and Dietary Habits in Hospitalized Patients with Schizophrenia : A Cross-Sectional Study. Medicina 57 : 255, 2021
38. Onaolapo OJ, Onaolapo AY : Nutrition, nutritional deficiencies, and schizophrenia : An association worthy of constant reassessment. WJCC 9 : 8295-8311, 2021
39. STROBE.
40. Yao S, Wang L, Yang Z, Xu Y, Zhang X, Shi Y, Cui D : Accelerated pace of frailty in patients with schizophrenia. The Journal of nutrition, health and aging 29 : 100412, 2025
41. Tsai M-T, Lee S-M, Chen H-K, Wu B-J : Association between frailty and its individual components with the risk of falls in patients with schizophrenia spectrum disorders. Schizophrenia Research 197 : 138-143, 2018
42. Harrington DM, Staiano AE, Broyles ST, Gupta AK, Katzmarzyk PT : Waist circumference measurement site does not affect relationships with visceral adiposity and cardiometabolic risk factors in children. Pediatric Obesity 8 : 199-206, 2013
43. Xu L, Zhang J, Shen S, Hong X, Zeng X, Yang Y, Liu Z, Chen L, Chen X : Association Between Body Composition and Frailty in Elder Inpatients. CIA Volume 15 : 313-320, 2020
44. Gingrich A, Volkert D, Kiesswetter E, Thomanek M, Bach S, Sieber CC, Zopf Y : Prevalence and overlap of sarcopenia, frailty, cachexia and malnutrition in older medical inpatients. BMC Geriatr 19 : 120, 2019
45. Liao Q, Zheng Z, Xiu S, Chan P : Waist circumference is a

better predictor of risk for frailty than BMI in the community-dwelling elderly in Beijing. Aging Clin Exp Res 30 : 1319-1325, 2018
46. Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K : Frailty, Body Mass Index, and Abdominal Obesity in Older People. The Journals of Gerontology Series A : Biological Sciences and Medical Sciences 65A : 377-381, 2010
47. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ : International Consensus Study of Antipsychotic Dosing. AJP 167 : 686-693, 2010
48. Woods SW : Chlorpromazine Equivalent Doses for the Newer Atypical Antipsychotics. J Clin Psychiatry 64 : 663-667, 2003
49. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M : Guidelines for the Pharmacotherapy of Schizophrenia in Adults. Can J Psychiatry 62 : 604-616, 2017
50. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML, Bloomfield MA, Bressan RA, Buchanan RW, Carpenter WT, Castle DJ, Citrome L, Daskalakis ZJ, Davidson M, Drake RJ, Dursun S, Ebdrup BH, Elkis H, Falkai P, Fleischacker WW, Gadelha A, Gaughran F, Glenthøj BY, Graff-Guerrero A, Hallak JE, Honer WG, Kennedy J, Kinon BJ, Lawrie SM, Lee J, Leweke FM, MacCabe JH, McNabb CB, Meltzer H, Möller HJ, Nakajima S, Pantelis C, Reis Marques T, Remington G, Rossell SL, Russell BR, Siu CO, Suzuki T, Sommer IE, Taylor D, Thomas N, Üçok A, Umbricht D, Walters JT, Kane J, Correll CU : Treatment-Resistant Schizophrenia : Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. AJP 174 : 216-229, 2017
51. Venkatasubramanian G, Danivas V : Current perspectives on chlorpromazine equivalents : Comparing apples and oranges! Indian J Psychiatry 55 : 207, 2013
52. Satake S, Arai H : Chapter 1 Frailty : Definition, diagnosis, epidemiology. Geriatrics Gerontology Int 20 : 7-13, 2020
53. Satake S, Shimada H, Yamada M, Kim H, Yoshida H, Gondo Y, Matsubayashi K, Matsushita E, Kuzuya M, Kozaki K, Sugimoto K, Senda K, Sakuma M, Endo N, Arai H : Prevalence of frailty among community-dwellers and outpatients in Japan as defined by the Japanese version of the Cardiovascular Health Study criteria. Geriatrics Gerontology Int 17 : 2629-2634, 2017
54. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, Popma JJ, Ferrucci L, Forman DE : Frailty Assessment in the Cardiovascular Care of Older Adults. Journal of the American College of Cardiology 63 : 747-762, 2014
55. The jamovi project., 2023
56. Faul F, Erdfelder E, Lang A-G, Buchner A : G*Power 3 : A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods 39 : 175-191, 2007
57. Wang Y, Shen S, Han P, Zheng K, Chen C, Wu Y, Huang C, Guo J, Qi Y, Chen X, Zheng Y, Xia X, Peng S, Guo Q : The association between visceral fat obesity and prefrailty in Chinese older adults : a cross-sectional study. BMC Endocr Disord 24 : 136, 2024
58. Li B, Li Y, Zhang Y, Liu P, Song Y, Zhou Y, Ma L : Visceral Fat Obesity Correlates with Frailty in Middle-Aged and Older Adults. DMSO Volume 15 : 2877-2884, 2022
59. Lee L, Patel T, Costa A, Bryce E, Hillier LM, Slonim K, Hunter SW, Heckman G, Molnar F : Screening for frailty in primary care : Accuracy of gait speed and hand-grip strength. Can Fam Physician 63 : e51-e57, 2017
60. Lin Y-H, Chen H-C, Hsu N-W, Chou P : Using hand grip strength to detect slow walking speed in older adults : the Yilan study. BMC Geriatr 21 : 428, 2021
61. Pham T, McNeil JJ, Barker AL, Orchard SG, Newman AB, Robb C, Ernst ME, Espinoza S, Woods RL, Nelson MR, Beilin L, Hussain SM : Longitudinal association between handgrip strength, gait speed and risk of serious falls in a community-dwelling older population. PLoS ONE 18 : e0285530, 2023
62. Chang C-Y, Lin M-H, Kuo C-C, Lu C-H, Wu D-M, Tsai M-K, Chu N-F : Nutritional Status and Renal Function in Relation to Frailty among the Community-Dwelling Elderly Taiwanese Population. The Journal of nutrition, health and aging 26 : 6-12, 2022
63. Konarzewska B, Stefańska E, Wendołowicz A, Cwalina U, Golonko A, Małus A, Kowzan U, Szulc A, Rudzki L, Ostrowska L : Visceral obesity in normal-weight patients suffering from chronic schizophrenia. BMC Psychiatry 14 : 35, 2014
64. Liu J, Fu L : Metabolic syndrome in patients with schizophrenia : Why should we care. Medicine 101 : e29775, 2022
65. Ryu K, Suliman ME, Qureshi AR, Chen Z, Avesani CM, Brismar TB, Ripsweden J, Barany P, Heimbürger O, Stenvinkel P, Lindholm B : Central obesity as assessed by conicity index and a-body shape index associates with cardiovascular risk factors and mortality in kidney failure patients. Front Nutr 10 : 1035343, 2023
66. Sugawara N, Yasui-Furukori N, Tsuchimine S, Fujii A, Sato Y, Saito M, Matsuzaka M, Takahashi I, Kaneko S : Body composition in patients with schizophrenia : Comparison with healthy controls. Ann Gen Psychiatry 11 : 11, 2012