



Relationship between anemia and its correlates and cognitive function in Chinese patients with chronic schizophrenia: A large cross-sectional study

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ABSTRACT

Background: Although both anemia and schizophrenia (SCZ) can cause cognitive decline, it is unclear whether anemia worsens cognitive decline in patients with SCZ. The primary objective of this study was to investigate the prevalence of anemia and the relationship between anemia, SCZ symptom severity, and cognitive function in patients with SCZ.

Methods: We obtained demographic and clinical data from 1690 inpatients with SCZ. All psychiatric symptoms and cognitive functioning were assessed by the Positive and Negative Syndrome Scale (PANSS), the Mini-Mental State Examination (MMSE), and the Repeated Battery for the Assessment of Neuropsychological Status (RBANS). Hemoglobin (HGB) values as well as red blood cell (RBC) counts were collected by routine blood tests.

Results: The proportion of anemia in patients with SCZ was 26.36 % (383/1453). Compared to SCZ patients without anemia, SCZ patients with anemia were older, had a lower bodyweight, a smaller waist circumference and lower apolipoprotein B levels, but longer QT intervals. Further logistic regression analysis revealed that anemia was associated with age, gender, and weight. In addition, there was no difference in cognitive function between SCZ patients with and without anemia.

Conclusion: Our findings suggest a high proportion of anemia in patients with chronic SCZ in the Han Chinese population. Several demographic and clinical variables are associated with anemia in SCZ patients.

1. Introduction

SCZ refers to a mental disorder characterized by psychotic symptoms such as hallucinations, delusions, and derangement of expression, as well as negative symptoms such as diminished motivation and expressiveness and cognitive deficits covering executive functions (Tandon et al., 2013). SCZ-related disorders affect approximately 1 % of the world's population and constitute one of the top ten global diseases (Orrico-Sanchez et al., 2020). A recent survey on the frequency of SCZ showed that the lifetime proportion of SCZ in China is 0.5 % (Insel, 2010). SCZ significantly reduces the ability of patients to work and assume appropriate social roles and is one of the leading causes of mental disability in China (Rao et al., 2021).

A person is considered anemic when their hemoglobin level or red blood cell count falls below standard levels (Newhall et al., 2020). About a quarter of the world's population is affected by anemia (Marton et al.,

2020; McLean et al., 2009). In the United States, the proportion of anemia in the general population averages about 5.71 % to 6.86 % (Wang and Wang, 2022). According to a survey, the prevalence of anemia among women in Jiangsu province, China, was 31.1 %. (Qin et al., 2013). The China Nutrition and Health Survey Program revealed that the proportion of anemia in a nationally representative sample in China was 14 %, with 18.5 % for women and 8.8 % for men (Zhan et al., 2014).

People who suffer from anemia produce oxygen shortages in tissues and organs, especially in the brain and heart, which can lead to difficulty concentrating, dizziness, and even fainting, with consequences for their daily life and performance (Deivita et al., 2021). In addition, there are several studies that have examined the relationship between anemia and cognitive decline. A meta-analysis discovered that patients with anemia could have a decline in cognition but did not find that anemia could significantly increase the risk of dementia (Kim et al., 2019). A study of

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Chinese middle-aged and elderly people found that anemia and low hemoglobin levels were significantly associated with cognitive decline (Qin et al., 2019). In another study, anemia and high white matter signals in the brain were associated with amnesic mild cognitive impairment in the elderly (Son et al., 2012).

To date, only a few investigations have reported on anemia in people with SCZ. For example, a follow-up study by Lee et al. showed that seven of 123 SCZ patients using clozapine at baseline were anemia, while 23 were anemia after two years of follow-up. The cumulative proportion during the two-year follow-up period was 24.5 % (Lee et al., 2015). Clozapine can induce anemia through three potential etiologies: First, the toxic metabolite hypothesis suggests that clozapine metabolism produces higher concentrations of toxic metabolites than the usual *N*-Desmethylclozapine. Second, the toxic free radical hypothesis asserts that neutrophils and their precursor stem cells can metabolize clozapine into harmful free radicals. The third reason is that clozapine may potentially lead to weight gain. In these patients with weight gain, factors such as imbalanced diet, increased iron demand, and low physical activity may play an important role in the occurrence of iron deficiency, which further increasing the risk of anemia. In another study, the proportion of anemia in SCZ patients was found to be 12.5 % (Wysocki and Szczepocka, 2018).

One potential cause of anemia in patients with schizophrenia is the side effects of antipsychotic medications. These medications are often used to control the symptoms of schizophrenia patients but can affect the production and longevity of red blood cells, which can lead to anemia. Furthermore, lifestyle factors such as malnutrition and unhealthy eating habits are prevalent among patients with chronic schizophrenia. Inadequate intake of essential nutrients, particularly iron, vitamin B12, and folate, can contribute to the development of anemia. The co-occurrence of anemia in patients with SCZ can be very damaging. Firstly, anemia makes it difficult for SCZ patients to choose antipsychotic medication as it may exacerbate the adverse effects of the medication (Grover et al., 2020). Secondly, anemia can lead to a reduction in the patient's ability to work and create barriers to the patient's return to social functioning (Brunner and Wullemin, 2010). Prolonged anemia can lead to physical weakness, difficulty concentrating, reduced communication with others and increased difficulty in treatment (Kassir, 2017). To date, no one has studied the proportion of anemia among Han Chinese SCZ patients (Kung et al., 2021; Yang et al., 2021). In addition, both SCZ and anemia can have an impact on patients' cognitive function. It remains unknown whether cognitive impairment is exacerbated when SCZ coexists with anemia. Therefore, the main aim of this study was to investigate the co-occurrence of anemia and its associated risk variables among patients with SCZ in the Han Chinese population. We hypothesized that (1) the proportion of anemia is higher in patients with SCZ and is associated with several clinical factors, and (2) there are differences in the performance of cognitive function between SCZ patients with and without anemia.

2. Methods

2.1. Subjects

We conducted a two-center retrospective cross-sectional study. We recruited 1690 inpatients with chronic SCZ from two psychiatric hospitals: Wuhan Psychiatric Hospital and Guangzhou Brain from December 2018 to December 2019. Of these 1690 patients, only 1462 had their hemoglobin values and red blood cell counts measured. Two patients had hemoglobin values >1000 g/L, and seven participants had hemoglobin values <10. These nine participants had possible recording biases and were not included in the analysis. Finally, a total of 1453 patients were included in this study. Of these participants, clozapine was used in 505 cases. All included participants had to meet the following criteria: (1) Chinese Han ethnicity, aged between 18 and 70 years; (2) diagnosis of SCZ by two experienced psychiatrists according to the

Structured Clinical Interview for DSM-IV (SCID); (3) duration of illness >5 years; (4) taking oral antipsychotic medication for >6 months prior to inclusion in this study; and (5) providing a written consent form.

We excluded participants from the study if they met the following criteria: (1) concurrent severe somatic or neurologically related illness; (2) pregnant or lactating women; (3) significant fluctuations in psychiatric symptoms within the past 2 weeks; and (4) inability to understand and fully complete psychometric assessments.

2.2. Sociodemographic and clinical characteristics

A detailed questionnaire was administered to obtain general information about the participants, including age, gender, education, marital status, smoking, height, weight, and waist circumference. Blood pressure was measured three times with a wristband sphygmomanometer while the participants were calm. Systolic and diastolic blood pressures were read and recorded, and the mean of the three measurements was taken as the final recorded parameter. All participants completed an electrocardiogram (ECG) test to record their heart rate (HR), QT interval, and QTC interval.

Participants' psychiatric symptoms were assessed by research psychiatrists trained in the use of the PANSS scale prior to the study. The PANSS scale consists of 30 items and includes three subscales: positive symptoms, negative symptoms, and general psychopathology. The interrater correlation coefficient of the PANSS total score was >0.8.

The Repeated Battery for the Assessment of Neuropsychological Status (RBANS) was administered by two clinical psychologists to measure the cognitive function of participants. The Repeated Battery for the Assessment of Neuropsychological Status (RBANS) measures several constructs of cognitive function, including attention, language, visuospatial/constructional abilities, and immediate and delayed memory. The RBANS consists of 12 tests, yielding 5 age-adjusted index scores and a total score. The RBANS has shown good reliability and validity in the general population as well as in patients with SCZ. In repeated assessments, the interrater correlation coefficient of the RBANS total score was 0.92.

2.3. Measurement of blood parameters

After an overnight fast, blood samples were collected from these participants between 7:00 and 9:00 am. Serum samples were refrigerated and transported on dry ice to the hospital's clinical laboratory center for testing. With complete confidentiality of the patient's clinical status, hospital laboratory technicians measured HGB, RBC, white blood cell count (WBC), serum albumin (ALB), serum globulin (GLO), and apolipoprotein A and B using an automated biochemical analyzer.

According to World Health Organization criteria, anemia is defined as hemoglobin <130 g/L in men and <120 g/L in women (Parricha et al., 2018). Mild anemia is defined as 91 g/L or higher, moderate anemia as 61–90 g/L, severe anemia as 31–60 g/L, and very severe anemia as 30 g/L.

2.4. Statistical analysis

We used percentages to express the proportion of anemia among patients with SCZ. A chi-square test was used to determine whether there were gender differences in the proportion of comorbid anemia in patients with SCZ. The chi-square test and ANOVA were used to assess differences in demographic, clinical, and laboratory parameters between anemic and nonanemic patients. Bonferroni correction was then used to adjust for multiple testing. Variables that differed significantly in one-way ANOVA or chi-squared tests were included in stepwise binary logistic regression (backward: Wald) to identify independent factors for comorbid anemia in patients with SCZ. The final variables for the stepwise backward logistic regression model included age, gender, weight, presence of diabetes, presence of hypertension, and QT interval.

The related variables used in this procedure included sociodemographic and biochemical variables (years of education, weight, height, waist circumference, PANSS total score, WBC, ALB, diastolic blood pressure). Further, multivariate linear regression analysis was conducted to detect the association of HGB with sociodemographic and biochemical variables. In addition, we used multivariate analysis of covariance to compare the cognitive performance of SCZ patients with and without anemia on the RBANS score. We used SPSS 25 to analyze the data. The significance level was set at 0.05, using two-tailed significant values.

3. Results

3.1. Proportion of anemia in SCZ patients

The overall prevalence of anemia in patients with SCZ was 26.36 % (383/1453) and it was significantly higher in female (30.49 %, 154/505) than in male (24.16 %, 229/948) ($\chi^2 = 6.82$, $df = 1$, $p = 0.009$).

There were significant age differences in the proportion of anemia in patients with schizophrenia ($\chi^2 = 88.9$, $p < 0.001$). Among young adults (aged 18–44 years), the proportion rate was 13.8 % (91/659), among middle-aged adults (aged 45–59 years), the proportion rate was 29.5 % (160/542), and among older adults (aged 60 years and older), the proportion rate was 42 % (103/245).

3.2. Clinical characteristics associated with co-morbid anemia in SCZ patients

Patients with anemia were older, had a lighter bodyweight, and had a slimmer waist circumference compared to patients without anemia (Bonferroni corrected all $p < 0.050$). In addition, patients with anemia had lower hemoglobin levels, reduced RBC counts, lower Apo B levels, and longer QT intervals on the ECG compared to patients without anemia (Bonferroni corrected all $P < 0.050$). We found no significant differences in positive symptoms, negative symptoms, and general psychopathology between schizophrenia patients with and without anemia. (Table 1)

As shown in Table 2, stepwise backward binary logistic regression was used to determine the parameters associated with comorbid anemia in patients with SCZ. We found the following variables were independently associated with anemia: age (OR = 1.048, $p \leq 0.001$, 95 % CI = 1.035–1.062), gender (OR = 1.755, $p = 0.001$, 95 % CI = 1.268–2.430), and weight (OR = 0.964, $p \leq 0.001$, 95 % CI = 0.954–0.975).

In addition, HGB was significantly associated with years of education ($r = -0.122$, $p < 0.001$), age ($r = -0.376$, $p < 0.001$), weight ($r = 0.304$, $p < 0.001$), height ($r = -0.260$, $p < 0.001$), waist circumference ($r = 0.195$, $p < 0.001$), PANSS total score ($r = -0.098$, $p = 0.004$), WBC ($r = 0.207$, $p < 0.001$), ALB ($r = 0.425$, $p < 0.001$), and diastolic blood pressure ($r = 0.137$, $p < 0.001$) in patients with SCZ (Bonferroni corrected all $P < 0.050$). Multivariate linear regression analysis showed that age ($B = -0.518$, $t = -8.159$, $p = 0.000$), weight ($B = 0.356$, $t = 5.934$, $p = 0.000$), years of education ($B = -0.603$, $t = -2.352$, $p = 0.019$).

3.3. Cognitive functioning between patients with SCZ with and without anemia

Table 3 shows no significant differences in the RBANS total and its 5 subscale scores, as well as the MMSE score, between SCZ patients with and without anemia (all $P > 0.05$). After adjusting for age, height, weight, waist circumference, PANSS total score, and blood results (WBC, ALB,GLO), there were still no significant differences in RBANS total and subscale scores, and MMSE score between the two groups (all $P > 0.05$).

4. Discussion

To the best of our knowledge, our study is the first to investigate the

Table 1

Socio-demographic as well as biochemical parameters featuring in subjects with schizophrenia with anemia vs. without anemia.

Variable	Patients with anemia (N = 383)	Patients without anemia (N = 1070)	F/Z/ χ^2	p
Age	50.96 ± 12.55	43.44 ± 12.85	-9.890	<0.001
Gender			6.82	0.009
Male, n (%)	229(59.8 %)	719(67.2 %)		
Female, n (%)	154(40.2 %)	351(32.8 %)		
Education (years)	9.39 ± 3.17	9.01 ± 3.19	1.545	0.123
Age of onset	26.26 ± 8.41	25.15 ± 8.02	-1.768	0.077
weight	62.71 ± 11.03	69.08 ± 13.11	-7.106	<0.001
Height	165.56 ± 21.12	165.31 ± 8.56	0.250	0.803
Waist	86.57 ± 12.93	90.64 ± 11.61	-4.684	<0.001
PANSS Total score	79.57 ± 16.16	79.22 ± 17.63	0.258	0.796
Positive symptoms	16.21 ± 4.94	16.50 ± 5.52	0.701	0.483
Negative symptoms	22.46 ± 6.78	21.95 ± 7.95	0.930	0.353
General psychopathology	40.90 ± 8.28	40.77 ± 8.68	0.194	0.846
Diabetes/no-Diabetes	78/305	112/958	24.311	<0.001
Hypertension/no-HP	57/326	91/978	12.541	0.001
WBC	6.69 ± 4.65	6.88 ± 1.93	-0.841	0.400
ALB	39.85 ± 4.35	43.18 ± 16.25	-2.973	0.003
APOB	0.79 ± 0.24	0.86 ± 0.26	2.757	0.006
GLO	25.02 ± 3.80	25.47 ± 11.28	0.386	0.699
QT	381.09 ± 33.71	369.93 ± 33.50	4.102	<0.001
QTC	420.52 ± 21.95	415.82 ± 37.28	1.711	0.087
HR	77.83 ± 12.83	78.33 ± 12.12	0.611	0.541
Systolic BP, mmHg	121.63 ± 10.93	122.01 ± 9.05	-0.463	0.643
Diastolic BP, mmHg	76.88 ± 6.72	78.00 ± 7.13	-1.887	0.060
BMI	23.33 ± 4.32	24.90 ± 4.92	5.510	<0.001
Typical/atypical antipsychotics	88/295	252/818	0.113	0.732
Daily AP dose (mg) (CPZ equivalent)	231.68 ± 214.67	278.32 ± 403.44	-1.886	0.060

Abbreviations: PANSS, Positive and Negative Syndrome Scale; HP, hypertension; HGB, hemoglobin; WBC, white blood cell; ALB, albumin; APOB, apolipoprotein B; GLO, globulin; HR, heart rate; BP, blood pressure; BMI, body mass index; AP, antipsychotics; CPZ, chlorpromazine.

Table 2

Factors relevant for anemia in subjects of schizophrenic disease.

	Wald statistic	p	OR	95 % CI
Age	52.486	<0.001	1.048	1.035–1.062
Gender	11.503	0.001	1.755	1.268–2.430
weight	39.72	<0.001	0.964	0.954–0.975

Table 3

Neurocognitive function of schizophrenic individuals with anemia versus schizophrenic individuals without anemia.

Variable	Patients with anemia (N = 227)	Patients without anemia (N = 643)	F/Z/ χ^2	p
MMSE Total score	22.75 ± 6.73	23.19 ± 6.06	1.977	0.059
RBANSS Total score	356.95 ± 55.59	360.33 ± 71.50	0.533	0.594
Immediate memory	54.76 ± 14.49	57.59 ± 27.35	1.220	0.223
Delayed memory	64.36 ± 18.80	64.26 ± 19.31	0.056	0.955
Visuospatial skills	77.91 ± 15.31	79.70 ± 18.47	1.189	0.236
Attention	77.73 ± 15.01	78.15 ± 15.14	0.297	0.767
Language	81.82 ± 12.67	79.51 ± 13.79	1.830	0.068

Abbreviations: MMSE, Mini-Mental State Examination; RBANS, Repeated Battery for the Assessment of Neuropsychological Status.

proportion of anemia and associated factors in Chinese Han patients with chronic SCZ. We had two main findings in this study. First, we found that 26.36 % of patients with chronic SCZ had anemia. Second, some demographic and clinical parameters were independently associated with anemia, including older age, a lower BMI, lower Apo B levels, and longer QT intervals.

The frequency of anemia in this study was higher in patients with SCZ compared to that in Poland (16.1 %) (Wysokinski and Szczepocka, 2018), elderly SCZ inpatients in Europe (21.1 %) (Bach et al., 2014; Wang and Wang, 2022), and the general population in China (14 %) (Zhan et al., 2014). Our result differs from previous studies, possibly because a different sample frame or different diagnostic criteria were used in this study. On the other hand, the high proportion of anemia in SCZ patients may be due to the following reasons: Firstly, chronic SCZ patients tend to suffer from malnutrition due to a chronically irregular diet, a lack of working ability, and poor family economic status (Zurron Madera et al., 2022). People with poor nutritional status tend to be more susceptible to anemia. Secondly, anemia is a side effect of some antipsychotic medications (Lally and MacCabe, 2015). However, chronic SCZ patients often require long-term antipsychotic medications to control their symptoms, which may lead to anemia in some susceptible patients with SCZ (Lee et al., 2015).

In addition, in the current study, we found gender differences in the proportion of anemia in patients with SCZ. Further logistic regression analysis confirmed that gender was an independent factor influencing anemia in SCZ patients. Women with SCZ were more likely to have comorbid anemia compared to men with SCZ. A study on eating disorders found that male patients were more likely to have anemia, which is inconsistent with the results of the present study (Nagata et al., 2022). However, this previous study differs from our current study on disease type. Moreover, the sample size of male patients was much smaller than that of female patients, which may have an impact on the extrapolation of the results. However, there is still a lack of research on gender differences in the proportion of anemia in patients with SCZ, and further research is needed.

In our study, age was found to be significantly and negatively associated with hemoglobin values in SCZ patients, and further logistic regression showed that age was independently associated with anemia. Several previous studies have shown that increasing age is associated with a higher risk of anemia (Ruan et al., 2019). A survey by Tettamanti et al. of elderly urban dwellers in Italy showed that increasing age was associated with an increase in the proportion of anemia (Tettamanti et al., 2010). A systematic review of the proportion of anemia in the elderly consistently found a trend towards increased anemia with increasing age (Rivilla Marugan et al., 2019). In a study of Mexican older adults, the highest proportion of anemia was found in those over 80 years of age (Contreras-Manzano et al., 2015). In this study, we found that patients with SCZ displayed a greater correlation between age and anemia, a phenomenon that may be due to the following reasons: First, patients with SCZ may gradually enter a period of chronic decline as they age, with varying degrees of decline in their ability to work, live, and care for themselves, making it difficult to meet their basic dietary needs (Khankeh et al., 2011). In such cases, patients are more likely to lose weight and become malnourished, which makes them more likely to develop anemia. Second, patients with SCZ often do not have adequate family and social support, and their financial problems are exacerbated by long-term medical costs (Chen et al., 2019). This means that they do not have enough money to buy food to meet their nutritional needs.

Further, we found that a lower weight was significantly associated with anemia in SCZ patients. This may be because lighter-weight patients are more susceptible to micronutrient deficiencies, such as those in iron and various vitamins, which may directly contribute to anemia (Schneider and Correia, 2020). A study of anemia in relation to body-weight in normal Chinese women found that obese individuals were less likely to be anemic than normal-weight patients, which is partially like our findings (Qin et al., 2013). Another study of secondary School

students in the Rabat region of Morocco showed that fat and anemia were more prevalent in overweight individuals, which contradicts our findings (Mehdad et al., 2022). The differences in these results may be due to differences in study populations, disease types, and ethnicity. However, no studies have examined the association between anemia and BMI in patients with SCZ, and therefore, more studies are still needed.

In this study, we found no differences in cognitive performance between patients with and without anemia, which contradicts our hypothesis. We speculate that the following factors may be responsible for this phenomenon: Cognitive impairment in SCZ is not exacerbated by anemia. Currently, there is a lack of research on the relationship between anemia and cognitive impairment in patients with SCZ. Therefore, further research is needed to explore the relationship between anemia and cognitive dysfunction in patients with SCZ.

Several experimental drugs for schizophrenia, including bitopertin and icleperitin (both GlyT1 inhibitors), cause anemia-like symptoms and may not be safe for cases with pre-existing anemia. Targeting such drugs to address anemia could have significant public health benefits. If any of these experimental drugs are approved, their potential impact on patients with pre-existing anemia must be considered. Addressing anemia in these cases could improve overall health and reduce the risk of adverse events associated with these drugs. Therefore, it is important that the safety of these medications in patients with anemia be thoroughly studied and evaluated before they are approved for use.

We are aware of several limitations of the study. First, the current study used a cross-sectional design, which prevented us from making causal inferences about anemia and associated factors in SCZ patients. Therefore, there is a need for a prospective study to further explore the causes and pathogenesis of anemia in patients with SCZ. Second, our study was a retrospective analysis using a single set of laboratory data rather than repeated measurements. Therefore, we were unable to determine whether the abnormal values of hemoglobin were long-term, chronic, or acute. Third, our study subjects were all chronic SCZ patients who were hospitalized for long periods of time. Therefore, the results of our study cannot be generalized to outpatients or community patients. Fourth, the patients in this study were all Han Chinese, and as anemia rates vary by race, our results cannot be applied to people of other races. In addition, we did not measure serum values for iron, vitamin B12, or folic acid, nor did we screen for thalassemia. For this reason, we were unable to further classify the anemia subtypes.

In conclusion, our findings suggest that the proportion of anemia is higher in patients with chronic SCZ. Age, gender, BMI, and RBC were independent risk factors for the development of anemia in patients with SCZ. Future studies on laboratory variables such as blood iron, vitamin B12, and folic acid will allow for a better understanding of the multifactorial pathophysiology of anemia in SCZ patients. Furthermore, due to the limitations of cross-sectional studies, the design of prospective studies is necessary to further confirm our findings.

CRediT authorship contribution statement

Yang Jiang: Formal analysis, Methodology, Writing – original draft. **Yi Cai:** Formal analysis, Methodology, Writing – original draft. **Yaoyao Lu:** Methodology, Writing – review & editing. **Guanghui Wu:** Writing – review & editing. **Xiang-Yang Zhang:** Conceptualization, Funding acquisition, Resources, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

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