Characterization of Anemia among Hospitalized Patients with Psychiatric Disorders

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ABSTRACT

Background: Anemia is associated with many psychiatric problems, including depression, bipolar disorder, schizophrenia, and other mental disorders. Moreover, anemia affects brain neurotransmitters, which affect learning, memory, and behavior.

Objective: The current study aims to shed light on the prevalence of anemia and its associated factors among hospitalized psychiatric patients.

Patients and Methods: A total of 143 admitted patients who had been diagnosed with psychiatric disorders with an age > 14-year-old who fulfilled the study criteria were enrolled in this cross-sectional study over six months in 2022. A structured clinical interview for the DSM-5 was used to settle the diagnosis of psychiatric disorders. Patients' data and blood samples were collected.

Results: About 27.27% of the psychiatric patients had anemia, with the highest frequency in schizophrenia (46.2%), followed by other disorders (33.3% bipolar, 10.3% schizoaffective, 5.1% depression, and 5.1% psychotic depression). Moreover, a higher frequency was found among adolescents and young adults than among older adults (76.9% vs. 23.2%). Normocytic normochromic morphology was the commonest subtype (59.0%).

Conclusion: Anemia could cause psychiatric symptoms or deteriorate an existing psychiatric condition when left untreated. So, it would be beneficial to catch up with the diagnosis of anemia in psychiatric patients and change the negative lifestyles and malnutrition habits of this population.

Keywords: Anemia, Psychiatric Disorders, Hemoglobin.

INTRODUCTION

Anemia is a medical disorder characterized by decreasing the hemoglobin (Hb) level and red blood cell (RBC) count. Male and non-pregnant females are diagnosed when their Hb falls below 13 g/dL and 12 g/dL, respectively [1]. In 2019, an estimated 1.8 billion individuals had anemia with various health consequences, including the immune system, neurocognitive function, and other diseases and other psychiatric problems [2].

Recent evidence links anemia with many psychiatric problems, including depression, bipolar, schizophrenia, and other mental disorders [3]. A previous study revealed that anemia influences brain neurotransmitter homeostasis, including dopamine, serotonin, and norepinephrine, which particularly affects learning, memory, and behavior [4].

Decreased iron level leads to significantly reduced concentration, expression and transport of norepinephrine, in addition to alteration to the level of norepinephrine protein receptors in the basal ganglia [5]. Moreover, patients with anemia experience symptoms like depression with mood and behavioral signs, especially those with microcytic anemia, and iron supplementation can cause recovery of brain neurotransmitters [6].

Nutritional deficiency as deficiency of folic acid and vitamin B12 had been linked to the severity of depressive disorder (DD) and there is no relation had been established between iron deficiency and DD.

However, the clinical manifestation of DD is affected by iron deficiency anemia (IDA) [7].

Thus, correction of nutrients deficient helps in prevention and treatment of DD as it causes recovery to the neurotransmitter and enzymes level [8]. However, the evidence for this relationship was addressed. Limited studies had investigated the characterization of anemia and its correlation with different clinico- demographic factors in psychiatric patients. Thus, the current study aims to study the prevalence of anemia and its associated factors among hospitalized psychiatric patients.

PATIENTS AND METHODS

Study design and participants

This hospital-based cross-sectional study that was conducted over six months in 2022 in the Psychiatry Department of a University-affiliated Hospital in Egypt. A total of 143 admitted patients diagnosed with psychiatric diseases as bipolar, schizophrenia, schizoaffective, depression and psychotic depression with an age > 14-year-old who fulfilled the study criteria were enrolled in the current study after the exclusion of patients with substance use disorders, active bleeding, recent blood transfusion, pregnancy, lactation, comorbid condition like infections, chronic hepatic or kidney disease, inflammatory, autoimmune and endocrinal disorders additionally patients unwilling to participate in the study (Figure 1).
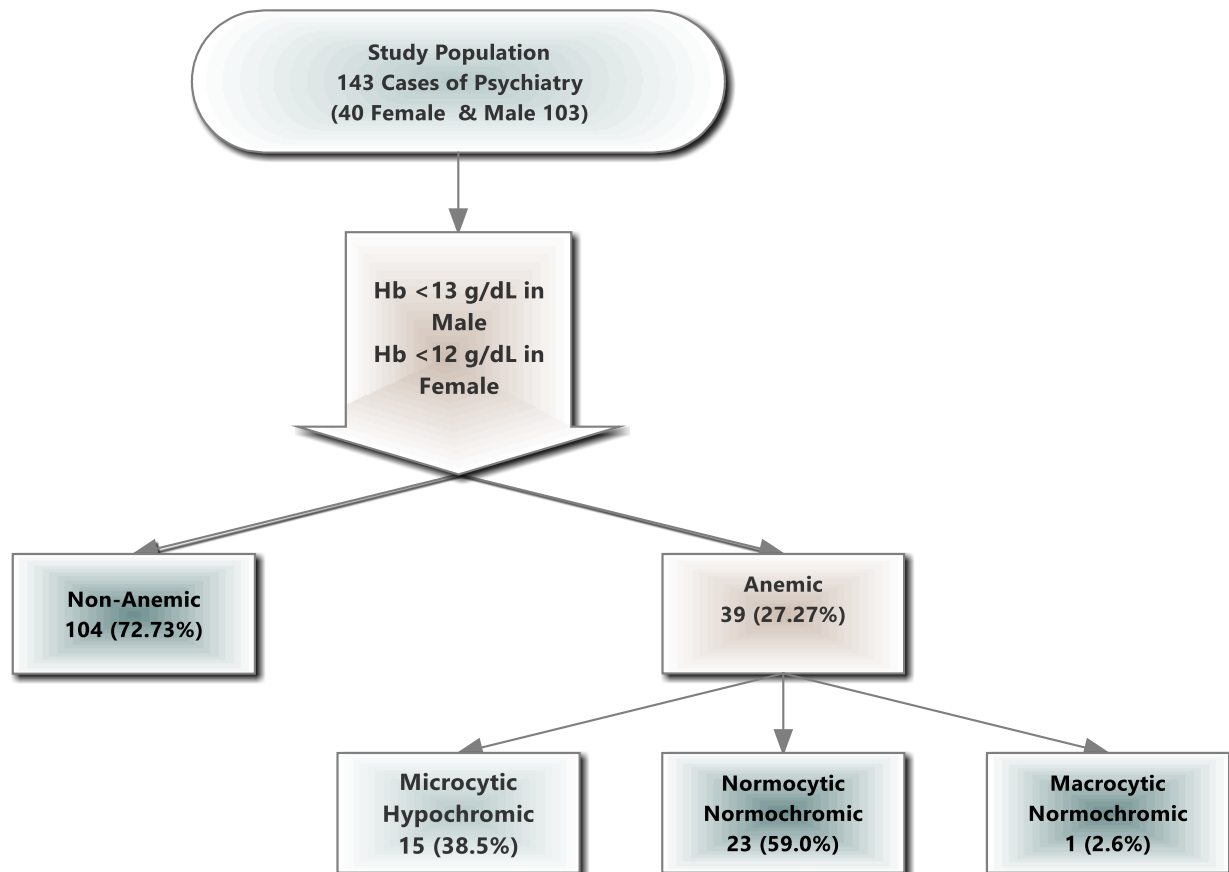
Figure (1): Algorithmic flow chart of the frequency of anemia and its subtypes (N=143)

Data collection and measures:
- Patients' personal information was collected using a structured questionnaire for **socio-demographic data** (age, sex, residence, level of education, marital status, occupation, drug abuse, smoking, chronic diseases, duration of illness, and family history of psychiatric disorders).
- To determine the diagnosis of psychiatric disorders, the Structured Clinical Interview for the DSM-5, clinical version (SCID-CV) was used. It takes the clinician through the DSM-5 diagnostic procedure step by step. Interview questions are easily placed next to each DSM-5 criterion, making it easier to rate each as present or absent. The SCID-5-CV is a shortened and reorganized version of the SCID Research Version, which is the structured diagnostic interview that researchers have used most often over the past 30 years to come up with DSM diagnoses [9].
- **Blood samples and hematological measures:** Samples of all enrolled individuals were collected within 24 h of hospitalization from the cubital vein. The Sysmex XN-1000 automatic hematology analyzer (Sysmex Corporation, Kobe, Japan) was used to measure hemoglobin (Hb) and mean corpuscular volume (MCV).
- Anemia was defined by the World Health Organization (WHO) as a hemoglobin (Hb) level less than 13 g/dL for males and 12 g/dL for non-pregnant females [1]. Anemia was further classified morphologically as microcytic (MCV 80 fL), normocytic (MCV 80-90 fL), and macrocytic (MCV > 90 fL) [10]. Finally, all patients diagnosed positive for anemia were linked to a hematologist for further management.

Sample size: a convenient sample size of all admitted patients fulfilling the selection criteria was used.

Ethical consideration:
Written consent had been taken from participants or their caregivers to participate in the study. Ethical approval was taken from the **Zagazig University Institutional Review Board number ZU-IRB#9922/7-3-2022.**

Statistical analysis
Data distribution was examined by the Shapiro-Wilk test. The Chi-square test was used to compare qualitative data expressed as numbers and relative percentages. The median, range, mean, and standard deviation (SD) were used to express quantitative data as indicated. For non-normally distributed data, the Mann-Whitney U test was employed to quantify the difference between quantitative variables in two groups, while the independent-t test was used for normally distributed

ones. One-way ANOVA F-test and Kruskal-Wallis Test were used to calculate difference between quantitative variables in more than two groups as indicated. Univariate and multivariate logistic regression analysis models were done. All statistical comparisons were two-tailed, with a P-value 0.05 reflecting a significant difference. The SPSS software version 24 was used for data analysis.

RESULTS
Study population characteristics
In terms of medical history, 72% were male and 77.6% were between the ages of 15 and 39. 4.2% and 5.6% had diabetes mellitus (DM) and hypertension, respectively. Drug abusers and smokers were 35.7% and 56.6%, respectively. By using the DSM-5, clinical version (SCID-CV), 51% had bipolar disorder and the rest of the participants (34.3%, 6.3%, 4.9%, and 3.5%) were diagnosed as schizophrenia, schizoaffective, depression, and psychotic depression, respectively.

Anemia on admission was found in 27.27% of our population, with a higher frequency among adolescents and young adults (AYA) than older adults (76.9% vs 23.2%), and more in university educated participants (61.5%).

Regarding the type of psychiatric illness, it was found that anemia was higher in schizophrenia (46.2%) than in other psychiatric diseases (33.3% bipolar, 10.3% schizoaffective, 5.1% depression, and 5.1% psychotic depression) and most of them (74.4%) were managed with atypical antipsychotic drugs (Table 1).

Table (1): Clinico-demographic data as regard the presensce of anemia on admission

Parameters		Anemia		Total N=143	P
		Absent N=104	Present N=39		
Age, years, median (range)		33 (16-76)	32 (15-53)	32 (15-53)	0.84
Age Group	AYA (15-39Y)	81 (77.9%)	30 (76.9%)	111 (77.6%)	0.902
	Older adults (≥ 40 y)	23 (22.1%)	9 (23.1%)	32 (22.4%)	
Sex	Female	21 (20.2%)	19 (48.7%)	40 (28.0%)	<0.001
	Male	83 (79.8%)	20 (51.3%)	103 (72.0%)	
Residence	Rural	66 (63.5%)	23 (59.0%)	89 (62.2%)	0.622
	Urban	38 (36.5%)	16 (41.0%)	54 (37.8%)	
Marital Status	Divorced	3 (2.9%)	3 (7.7%)	6 (4.2%)	0.347
	Married	49 (47.1%)	15 (38.5%)	64 (44.8%)	
	Single	52 (50.0%)	21 (53.8%)	73 (51.0%)	
Occupation	Manual	29 (27.9%)	7 (17.9%)	36 (25.2%)	0.136
	Mental	33 (31.7%)	9 (23.1%)	42 (29.4%)	
	Unemployed	42 (40.4%)	23 (59.0%)	65 (45.5%)	
Education	Read/write	3 (2.9%)	1 (2.6%)	4 (2.8%)	0.525
	School	48 (46.2%)	14 (35.9%)	62 (43.4%)	
	University	53 (51.0%)	24 (61.5%)	77 (53.8%)	
Drug abuse		42 (40.4%)	9 (23.1%)	51 (35.7%)	0.054
Smoking		66 (63.5%)	15 (38.5%)	81 (56.6%)	0.007
Diabetes		4 (3.8%)	2 (5.1%)	6 (4.2%)	0.733
Hypertension		6 (5.8%)	2 (5.1%)	8 (5.6%)	0.882
Type of illness	Bipolar	60 (57.7%)	13 (33.3%)	73 (51.0%)	0.123
	Schizophrenia	31 (29.8%)	18 (46.2%)	49 (34.3%)	
	Schizoaffective	5 (4.8%)	4 (10.3%)	9 (6.3%)	
	Depression	5 (4.8%)	2 (5.1%)	7 (4.9%)	
	Psychotic Depression	3 (2.9%)	2 (5.1%)	5 (3.5%)	
Duration of illness in years, median (range)		4 (0.1-30)	5 (0.1-21)	5 (0.1-30)	0.467
Family History of illness		28 (26.9%)	10 (25.6%)	38 (26.6%)	
Type of anti-Psychotic drugs	Atypical	58 (55.8%)	29 (74.4%)	87 (60.8%)	0.099
	Combined	43 (41.3%)	10 (25.6%)	53 (37.1%)	
	Typical	3 (2.9%)	0 (0.0%)	3 (2.1%)	
Type of anemia	Normocytic normochromic	-	23 (59.0%)		
	Microcytic hypochromic	-	15 (38.5%)		
	Macrocytic normochromic	-	1 (2.6%)		

Qualitative variables were expressed as numbers and percentages.

Anemic group analysis

There was a highly statistically significant difference in Hb and hematocrit levels regarding gender as it was more predominant in males than females (Table 2).

The difference in hematological profile between both anemic and non-anemic participants regarding smoking, age difference, and type of diagnosed psychiatric illness was statistically significant. There was a statistically significant increase in MCV in the majority of smokers with anemia and no difference in hematological profile based on age difference and type of illness (Table 2, 3).

Table (2): Comparison of hematological profile in patients with anemia bases on sex, age, and smokers

	Sex		P	Age Group		P	Smokers		P
	Female	Male		AYA (15-39Y)	Older adults (≥ 40 y)		No	Yes	
WBC, x10⁹/L	8.89±2.22	8.32±2.01	0.633	8.70±2.11	8.26±2.06	0.653	8.76±1.91	8.34±1.84	0.648
Hb, g/dL	11.18±0.58	12.54±0.53	<0.001	11.86±0.90	11.93±0.87	0.894	11.68±0.83	12.20±0.90	0.046
Hct %	34.76±2.17	38.51±1.69	<0.001	36.66±2.82	36.78±2.41	0.855	36.16±3.07	37.53±1.76	0.067
MCV, fL	80.27 (62.3-89.1)	82.8 (63.1-114.2)	0.169	82.50 (62.3-91.8)	80.80 (69.3-114.2)	0.453	78.36±8.07	85.14±10.01	0.026
MCH, Pg	25.71 (19.3-30.5)	27.10 (18.9-34)	0.144	26.70 (18.9-31.1)	26.20 (22.6-34)	0.56	25.96 (18.9-30.5)	27.50 (22.6-34)	0.081
MCHC g/dL	32.60 (27.1-34.8)	32.75 (29.8-34.9)	0.789	32.65 (27.1-34.9)	32.60 (30.4-33.9)	0.593	32.6 (28.4-34.8)	32.98 (27.1-34.9)	0.435
RDW %	14.1 (12.7-19.9)	13.85 (12.3-19.7)	0.822	13.90 (12.3-19.9)	13.90 (13.3-17.9)	0.333	14.3 (12.3-19.9)	13.8 (12.7-17.5)	0.254
RBCs x10⁶/mm³	4.30 (3.7-6.3)	4.7 (3.2-6.7)	0.092	4.40 (3.7-6.7)	4.70 (3.2-5.6)	0.535	4.50 (3.70-6.70)	4.40 (3.20-5.40)	0.684
Platelet, x10⁹/L	260 (10-358)	232.5 (14-390)	0.423	237 (100-355)	260 (205-390)	0.182	238 (100-358)	255 (140-390)	0.444

Continuous variables are described as mean± SD for normally disturbed variables and median (range) for non-normally disturbed variables.

Table (3): Hematological profile in patients with anemia as regard the type of psychiatric illness

	Type of psychiatric illness					Sig.
	Bipolar	Depression	Psychosis	Schizoaffective	Schizophrenia	
WBC, x10⁹/L	8.30±1.91	5.70±1.41	11.80±2.45	9.45±1.77	8.58±2.11	0.244
Hb, g/dL	12.2±0.81	11.20±0.71	10.35±0.7	12.30±0.62	11.93±0.89	0.063
Hct%	37.1±3.17	33.70±1.27	35.45±4.3	38.43±1.37	36.53±2.39	0.319
MCV, fL	81.50 (62.3-86.9)	84.35 (84.2-84.5)	82.5 (75-89.1)	79.55 (76.2-81)	82.20 (63.9-114.2)	0.829
MCH, pg	26.53 (18.9-3)	285 (27.6-28.5)	245 (23.9-24.2)	25.80 (24.6-26.7)	27 (19.3-34)	0.732
MCHC g/dL	32.70 (29.8-34.9)	32.95 (32.1-33.8)	29.30 (27.1-31.5)	31.55 (31.3-33)	32.85 (28.4-34.1)	0.062
RDW %	14.10 (12.9-19.7)	12.90 (12.7-13.1)	16.80 (13.7-19.9)	13.70 (13.3-14.7)	14 (12.3-17.9)	0.272
RBCsx10⁶/mm³	4.40 (4-6.7)	4 (3.9-4.1)	4.30 (4.3-4.3)	4.75 (4.7-5.2)	4.45 (3.2-6.3)	0.411
Platelets, x10⁹/L	240 (153-326)	262.50 (255-27)	328.50 (302-355)	225 (21-235)	236 (10-39)	0.376

Continuous variables are described as mean± SD for normally disturbed variables and median (range) for non-normally disturbed variables.

Univariate and multivariate logistic regression analysis:

After performing univariate and multivariate logistic regression analysis to detect the potential independent predictors of anemia among psychiatric patients, smoking was found to be a protective factor, while gender is one of the predictors of anemia (Table 4).

Table (4): Univariate and multivariate logistic regression of potential predictors of anemia in admitted patients with psychiatric illness

Co-variate	Univariate analysis			Multivariate analysis		
	Sig.	OR	95% C.I. for OR	Sig.	OR	95% C.I. for OR
Age Group (AYA Vs Older adults)	0.902	1.06	0.44-2.54			
Sex (Female Vs Male)	**0.001**	3.75	1.70-8.27	**0.028**	3.17	1.13-8.89
Residence (Urban Vs Rural)	0.622	0.83	0.39-1.76			
Drug abuse (Yes Vs No)	0.058	0.44	0.19-1.03			
Smoking (Yes Vs No)	**0.008**	0.36	0.17-0.77	0.406	0.66	0.25-1.76
Diabetes (Yes Vs No)	0.734	1.35	0.24-7.69			
Hypertension (Yes Vs No)	0.882	0.88	0.17-4.57			
Type of illness (Bipolar reference)						
Depression	0.059	0.37	0.16-0.86			
Psychotic depression	0.675	0.69	0.12-3.92			
Schizoaffective	0.886	1.15	0.18-7.53			
Schizophrenia	0.662	1.38	0.33-5.80			
Duration of illness	0.537	1.02	0.96-1.07			
Family History of illness (Yes, Vs No)	0.877	0.94	0.40-2.17			
Type of anti-psychotic (Atypical Vs. Typical containing)	**0.046**	0.43	0.19-0.98	0.063	0.43	0.17-1.05

All variable with P-value <0.05 in univariate analysis were entered in multivariate logistic regression model, OR: odds ratio; 95% C.I.: 95% confidence interval.

DISCUSSION

There is a dynamic relationship between anemia and psychiatric disorders. Anemia, when untreated, could cause not only physical but also psychiatric symptoms, such as cognitive dysfunction and depression. But also, its coexistence with psychiatric diseases could cause certain complications or aggravation in the severity of the preexisting condition in these patients [11].

As regards the frequency of anemia, anemia was found in 27.27% of the hospitalized psychiatric patients. However, earlier studies reported several rates of anemia in those patients: 25.4%, 12.2%, and 6% [12]. In our study, the frequency of anemia was higher in schizophrenia (46.2%) than in other psychiatric diseases (33.3% bipolar, 10.3% schizoaffective, 5.1% depression, and 5.1% psychotic depression). Low hemoglobin levels are linked to depression, which could be caused by physical health problems like fatigue [13], low levels of oxygen in the brain [14], a lack of vitamin B12 [15], or higher levels of inflammation [16].

As regards the types of anemia, in the current study, the commonest morphological pattern was normocytic normochromic anemia (59.0%) of anemic cases, which could be anemia of inflammation [17], antipsychotic-induced [18], or even early IDA [19]. Regarding atypical antipsychotic related anemia, there has been a near significant difference in the anemic Vs. non anemic group (74.4% Vs. 55.8%, respectively). Clozapine initiation was found to have a high incidence of anemia in psychiatric patients, especially in the first two years of treatment, and it is considered as a marker of inflammation due to its effect on C - reactive protein (CRP) and acute phase reactant. Therefore, it is possible to be cofounder in the pathogenesis of the type of anemia. This may be explained in 59% of the anemic patients of anemia of inflammation described in normocytic-normochromic anemia [18]. It was known that clozapine at the initiation of treatment led to the elevation of CRP level, causing transient anemia unrelated to age, smoking and race [20]. **Lozano et al.** [21] in the previous study showed the prevalence of anemia in relation to time in clozapine treated patients.

Furthermore, microcytic hypochromic anemia was encountered in (38.5%) of anemic cases, most probably reflecting IDA. That was associated with unipolar depressive disorder in prior studies, possibly through iron deficiency (ID) that alters the monoamine key neurotransmitters of mood such as dopamine, serotonin, and noradrenalin [22]. Lower serum ferritin concentrations were significantly correlated with depressive symptoms [23].

However, there were only seven depressed and five psychotic depressive patients who participated in this study, which may reflect quite lower figures when compared to the findings reported in the literature. This is consistent with **Korkmaz et al.** [24] where anemia was found in 35% of psychotic disorder patients, 22% of depression patients, and 25% of bipolar disorder patients.

Emotional dysregulation has been deemed as one of the core neuropsychological pathologies of bipolar disorder [25]. It has been well documented that iron is associated with socioemotional development and that ID may disturb the development of emotional regulation [26].

Wan-Kim et al. [27] demonstrated that IDA was significantly more in patients with prominent negative schizophrenic symptoms. They hypothesized that iron dysregulation and depletion are associated with changes in dopaminergic activity. The tyrosine hydroxylase enzyme uses iron as a cofactor and acts as an important limiting step in dopamine synthesis. Alterations in dopamine synthesis are associated with many neurological diseases [28]. We also found the most anemic psychiatric patients were jobless (59.0%) and lived in rural districts (59.0%), subsequently having little access to psychiatric centers and having difficulties expressing physical symptoms. These results match those observed by **Korkmaz et al.** [24]. Thus, it is inevitable that the rate of anemia among psychiatric patients will be higher than the general population.

In chronic mental patients, a concomitant physical disease, in addition to the underlying disorder, is common [29]. This coexistence lowers the quality of life of the patients, lengthens the psychiatric treatment period, and may potentially increase morbidity and mortality. Factors such as negligence of physical symptoms by mental healthcare professionals, in addition to assessment of physical complaints as psychosomatic, reluctance of no psychiatric physicians to provide services to psychiatric patients, lack of time and resources for checkups in mental health services, and patients' inefficiency in explaining their medical problems, as well as difficulties related to implementing changes in their lifestyle, could prevent psychiatric patients from receiving the appropriate health care services [30].

Anemia in chronic psychiatric patients is caused by treatment-related factors, drugs taken, physical conditions, bad lifestyle habits, and nutritional disorders. Detailed identification of the physical symptoms of psychiatric patients and providing them with health care services, especially those who experience problems in expressing their complaints and are often labeled by society, is quite important for early diagnosis and treatment [24].

Although anemia in chronic psychotic patients may be attributed to many demographic factors, including age, gender, residence, education, and marital status, in this study by univariate and multivariate analysis, gender was found to be an independent risk factor for anemia (P = 0.028, OR = 3.17). Surprisingly, despite significantly higher levels of Hb and Hct% (P 0.001) in males, anemia was found to be more prevalent in males than females, in contrast to other studies that revealed an increase in the frequency of anemia among females during the child-bearing period [7-13]. A possible explanation for this is that the majority of the population were males (72% versus 28% females). Moreover, antipsychotics-induced amenorrhea and menstrual irregularities were reported in 15–97% of women receiving antipsychotics [31].

We found the high prevalence of anemia among adolescents and young adults (76.9% vs 23.2%, respectively). That could be explained by the fact that the majority of our study population were AYA (77.6%), having a rapid growth rate with increasing iron ferritin consumption [32].

However, another study found a high prevalence of anemia among older adults due to poor socioeconomic status, low educational level, and unmarried status, all of which are associated with a variety of negative outcomes on mood and cognitive function [33].

Smoking was one of the potential protective factors against anemia in patients with psychiatric disorders in univariate analysis (P = 0.008, OR; 0.17–0.77), but failed to independently affect anemia in the multivariate module. **Lee et al.** [34] revealed smoking as one of the significant protective factors against anemia, especially in patients with atypical antipsychotic drugs as smoking causes elevation of Hb level and other hematological profiles due to reducing oxygen tension in the body by carbon monoxide, which consistently increases the release and maturity of erythrocytes. Other researchers discovered a significant increase in Hb, RBC, WBC, MCH, and MCV in smokers with anemia, with a high percentage found in mild smokers, and the number of anemic patients decreased with severity of smoking, with an increase in the level of MCV and MCHC, as smoking was implicated in macrocytosis by altering folic acid and vitamin B12 [35]. In this study, the significant increases in Hb, MCHC, and Hct% in the majority of smokers could be explained by the

antiapoptotic influence of hypoxia and increased iron release from the liver resulting from inhibition of hepcidin [16].

Limitations and recommendations:

To the best of our knowledge, this study is the first in Egypt and the Middle East Region to focus on the identification of the prevalence of anemia and its morphological subtypes among psychiatric patients with a relatively acceptable sample and the inclusion of different interview-based psychiatric diagnoses.

However, there are several limitations to this study that should be mentioned. Due to the cross-sectional design of this study, no causal relationship could be investigated in the association between anemia and psychiatric disorders. Thus, we recommend further multicenter prospective studies with a larger sample size to identify a possible causal relationship through assessment of etiological causes of anemia and its proper management and follow-up as well as its impact on psychiatric illness' outcome.

Finally, a multidisciplinary management approach to monitor blood profiles, improve eating habits, and change the lifestyle of psychiatric patients is recommended.

CONCLUSION

Anemia could cause psychiatric symptoms or deteriorate an existing psychiatric condition when left untreated. So, it would be beneficial for health professionals to catch up with the diagnosis of anemia in psychiatric patients and change the negative lifestyles and malnutrition habits of this population.

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