

Is Vitamin B12 Level a Reliable Predictor of Psychosis Severity in Male Patients with Megaloblastic Anemia at a Single Tertiary Hospital?

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Background: Megaloblastic anemia (MA) occurs due to ineffective erythropoiesis, which results from impaired DNA synthesis in the hematopoietic precursors and intramedullary hemolysis. MA's most common cause is nutritional deficiencies of either cobalamin (vitamin B12) or folate (vitamin B6). This study aims to determine the association between MA caused by vitamin B12 deficiency and psychosis among psychotic male patients in Mental Health Hospital at Taif, Saudi Arabia.

Methods: Fifty psychotic male patients, aged 48.58±1.72, were recruited from the Mental Health Hospital at Taif, Saudi Arabia, in addition to 54 sex-matched healthy controls. The following tests were run: complete blood count (CBC), liver function tests (LFT), serum levels of vitamin B12, folate, and C-reactive protein (CRP).

Results: The CBC showed that RBCs count, haemoglobin, haematocrit, platelets count, mean platelets volume (MPV), and absolute lymphocyte count were significantly lower in psychotic patients versus healthy controls (P=0.007, P=0.002, P=0.001, P=0.004, P=0.0001, and P=0.005, respectively). In contrast, the eosinophil absolute count and basophil percentage were significantly higher in psychotic patients versus controls (P=0.009, P=0.0001, respectively). Vitamin B12 levels were insignificantly decreased in psychotic patients versus healthy group. There were significant negative correlations between serum levels of VitB12 and negative symptoms (r=-0.381, P=0.006) and hallucination (r=-0.297, P=0.036).

Conclusion: These findings indicate no link between MA induced by VitB12 insufficiency and psychosis among psychotic patients. However, low serum VitB12 can predict the severity of some psychosis signs, including hallucinations and negative symptoms. Therefore, monitoring VitB12 levels and its supplementation in psychotic patients is recommended to improve their symptoms.

Keywords: vitamin B12, complete blood count, megaloblastic anemia, psychosis

Introduction

Anemia is a condition where red blood cell (RBC) count and haemoglobin (HBG) concentration are lower than the reference range, resulting in decrease in the oxygen-carrying capacity, which is not meeting an individual's physiological needs. Decrease HBG concentration and haematocrit (HCT) are the most common haematological parameters used to diagnose anemia. In addition, RBC count, mean corpuscular volume (MCV), reticulocyte count, examination of blood film, and HBG electrophoresis are considered significant parameters in anemia diagnosis.¹

Megaloblastic anemia (MA) is a condition that occurs due to ineffective erythropoiesis (RBC production), which results from impaired DNA synthesis in the hematopoietic precursors and intramedullary hemolysis. The hallmark of MA is increased MCV, leading to macrocytosis features of RBCs. In addition, thrombocytopenia, as well as leukopenia, are presented frequently in MA.² MA incidence has increased in the last two decades, particularly in underdeveloped countries.³ In India, megaloblastic anemia is a very common condition, with prevalence ranging from 2–40%.⁴

Megaloblastic anemia's most common causes include nutritional deficiencies of either cobalamin (vitamin B12) or folate (vitamin B6).²

MA clinical symptoms include weakness, fatigue, dizziness, shortness of breath, tachycardia and pale skin. In addition, MA can cause gastrointestinal symptoms, including sore tongue, gum bleeding, weight loss, stomach upset, constipation, and diarrhea. Furthermore, MA results in nerve cell damage, which manifests as numbness or tingling in fingers and toes, walking difficulty, memory loss, mood swings, disorientation, depression, and dementia in severe cases.⁵ MA is considered the main feature of vitamin B12 deficiency, which is associated with psychosis, mood, cognitive, and neurologic symptoms.^{6,7} Psychosis is a condition that can be defined in one or more of five domains: hallucinations, delusions, abnormal motor behaviors including catatonia, disorganized speech, and thinking, and negative symptoms.⁸ Neuropsychiatric symptom incidence among individuals diagnosed with vitamin B12 deficiency is 4–50%. In addition, over more than a hundred years, many case reports and other studies have described an association between vitamin B12 and psychosis symptoms.⁷

A complete blood count (CBC) test is affordable and can be easily made. Leukocytes perform different tasks in immune system.⁹ Changes in leukocyte count reflect immune system reaction in inflammation.⁹ Neutrophil–lymphocyte ratio (NLR) is an important marker of chronic and low-grade inflammation and clinical outcomes in neuroimmune disorders.^{10–12} Monocytes are sources of several cytokines and directly affect platelets and endothelial cells, which induces prothrombotic and proinflammatory pathways. Inflammatory process may be part of schizophrenia etiology.^{13–15} Platelets are another structure included in proinflammatory secretion with leukocytes. Platelet–lymphocyte ratio (PLR) is used as simple indicator that correlates with inflammation, cardiovascular and chronic diseases.^{10–12,16} Peripheral platelet models are utilized as indicators of central serotonin (5-HT) metabolism, as they reflect central serotonergic functions.¹⁷ Serotonin is involved in the pathophysiology of psychotic disorders and plays pivotal roles in regulation of platelet aggregation and vascular tone.¹⁸ Abnormal platelet counts and mean platelet volume (MPV) parameters are determined in some psychiatric disorders, including bipolar disorder, unipolar depression, and schizophrenia.^{10,19,20} Patients with some psychiatric disorders have raised platelet counts.^{18,21} Varsak et al²² found that the NLR was significantly higher in first episode psychosis (FEP) versus control groups.

Thus, the current study hypothesizes an association between MA caused by vitamin B12 deficiency and psychosis. Studying this association will help the psychiatric specialist improve the psychosis patient's symptoms and raise the knowledge level of how poor diet and vitamin B12 deficiency could affect an individual's mental health.

This study aims to determine the association between megaloblastic anemia and psychosis among psychotic male patients in the Mental Health Hospital at Taif.

Materials and Methods

Study Design and Population

The current study is a case-control study performed among inpatients showing psychosis symptoms in Mental Health Hospital at Taif, Saudi Arabia. The study followed the ethical standards of the Taif Ethics Research Committee at the hospital. The study was made in accordance with principles of the Declaration of Helsinki. Informed consent was obtained from the healthy control study participants prior to study commencement. Psychosis patients often lack insight into their medical condition and possible treatments and thus are unable to provide consent. It was therefore necessary to obtain written informed consent from the patients' relatives. The study was approved by Taif Ethics Research Committee approval number (471–2021).

Fifty male adult inpatients were included, with their age range between 28–82 years, in addition to 54 age-matched healthy male controls. All inpatients and control participants in the present study are males from Saudi Arabia.

Inclusion criteria were being psychotic inpatients >18 years old showing psychosis symptoms diagnosed by a psychiatrist. Excluded from the study were inpatients taking vitamin B12 supplements, vegetarian, alcoholic, history of gastric surgery such as bariatric surgery. Also patients with chronic diseases that cause megaloblastic anemia like Crohn's disease, celiac disease pancreatic insufficiency, congenital intrinsic factor deficiency, and patients on drugs that induce megaloblastic anemia, proton pump inhibitors, metformin, anticonvulsants, cytotoxic.

Method

Blood samples were collected from participants. Psychiatrist made a psychiatric diagnosis of psychosis and determined the severity of psychosis symptoms at the hospital. In addition, psychiatric specialists interviewed participants to determine the psychosis symptoms severity using the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Clinician-Rated Dimensions of Psychosis Symptom Severity is an 8-item measure that assesses the severity of mental health symptoms that are important across psychotic disorders, including disorganized speech, cognitive impairment, negative symptoms, psychomotor activity abnormality, delusions, hallucinations, mania, depression. Each domain scale ranges from 0 to 4: 0 = not present; 1 = equivocal (occasionally elevated, expansive or irritable mood or some restlessness); 2 = present but mild (frequent periods of somewhat elevated expansive or irritable mood or restlessness); 3 = present but moderate (frequent periods of extensively elevated, expansive, or irritable mood or restlessness); and 4 = present and severe (daily and extensively elevated expansive or irritable mood or restlessness). Negative symptoms include loss of interest in or enjoyment of daily activities, loss of motivation, withdrawal from social life, difficulty showing emotions, difficulty functioning normally.

Inpatients' blood samples were collected in two tubes: EDTA tubes for CBC analysis and lithium heparin tubes for clinical chemistry analysis as liver function tests, C-reactive protein, vitamin B12 and folic acid level measurements. Lithium heparin samples were centrifuged at 4000 rpm for five minutes, and then plasma was separated into two aliquots. Inpatients' EDTA samples and LH aliquots were transported on ice to keep the sample temperature between 2–8 °C from Mental Health Hospital in Taif to King Faisal Medical Complex in Taif City. Both inpatients' EDTA samples and LH aliquots were analyzed within two hours of collection.

Statistical Analysis

The data were analyzed utilizing IBM SPSS Statistics for Windows, version 23 (IBM SPSS, IBM Corp., Armonk, N.Y., USA). Shapiro–Wilk test was utilized to evaluate normal value distribution. The collected values were presented as mean \pm standard deviation (SD), minimum and maximum. Statistical comparisons of parametric data were made by unpaired student *t*-test for normally distributed data and Mann–Whitney test for abnormally distributed data. Correlations between components of DSM-5 and serum levels of vitamin B12 were made using Spearman correlation. $P < 0.05$ was considered statistically significant.

Results

Sociodemographic Data

The mean age of patients and controls was 48.58 ± 1.72 and 48.58 ± 1.72 years. The mean BMI of patients and controls was 27.66 ± 0.83 and 26.22 ± 0.64 (kg/m²), respectively. All inpatients included in the study were schizophrenic, showing psychosis symptoms. The psychiatric disorder percentages of those showing psychotic symptoms were as follows: schizophrenia (98.0%) and schizo-affective disorder (2.0%). Intellectual disability was confirmed in 12.0% of the inpatients included in the study along with schizophrenia. Medical disorders were ischemic heart diseases (14.0%), hypertension (14.0%), hyponatremia (12.0%), diabetes mellitus (10.0%), epilepsy (10.0%), hypothyroidism (4.0%) and others (40.0%).

Medications Used by the Patients

Psychotic medications used by the patients are shown in [Table 1](#). The most used medications were Aripiprazole (32%) then Olanzapine (30%), Lorazepam (28%) and Haloperidol (24%).

Clinician-Rated Dimensions of Patients' Psychosis Symptom Severity (DSM-5)

Clinician-rated dimensions of patients' psychosis symptom severity (DSM-5) was shown in [Table 2](#). The highest score was for disorganized speech (1.64 ± 0.21 [0–4]), followed by cognitive impairment (1.38 ± 0.17), negative symptoms (1.22 ± 0.15), psychomotor activity abnormality (1.06 ± 0.16), delusions (0.86 ± 0.15), hallucinations (0.78 ± 0.13), mania (0.52 ± 0.13) and, lastly, depression (0.26 ± 0.09). The total score ranged from 0 to 25, with a mean score of 8.02 ± 0.70 .

Table 1 Medications Used by the Patients

Medications	Classification	Patients (N=50)
Atypical antipsychotic		
Aripiprazole	Atypical antipsychotic	16 (32.0%)
Olanzapine	Atypical antipsychotic	15 (30.0%)
Clozapine	Atypical antipsychotic	5 (10.0%)
Quetiapine	Atypical antipsychotic	2 (4.0%)
Risperidone oral	Atypical antipsychotic	2 (4.0%)
Risperidone, long-acting	Atypical antipsychotic	2 (4.0%)
Paliperidone	Atypical antipsychotic	2 (4.0%)
Quetiapine XR	Atypical antipsychotic	1 (2.0%)
Amisulpride	Atypical antipsychotic	1 (2.0%)
Fluphenazine, long-acting	Atypical antipsychotic	1 (2.0%)
Typical antipsychotic		
Haloperidol	Typical antipsychotic	12 (24.0%)
Trifluoperazine	Typical antipsychotic	3 (6.0%)
Chlorpromazine	Typical antipsychotic	3 (6.0%)
Haloperidol, long-acting	Typical antipsychotic	1 (2.0%)
Antidepressants		
Mirtazapine	Antidepressant	1 (2.0%)
Escitalopram	Antidepressant	2 (4.0%)
Amitriptyline	Antidepressant	1 (2.0%)
Agomelatine	Antidepressant	2 (4.0%)
Benzodiazepines		
Clonazepam	Benzodiazepine	7 (14.0%)
Lorazepam	Benzodiazepine	14 (28.0%)
Anticonvulsants		
Carbamazepine	Anticonvulsant	1 (2.0%)
Valproate as psychiatric medicine	Anticonvulsant	5 (10.0%)
Valproate medicine including use as psychiatric and epileptic medicine	Anticonvulsant	8 (16.0%)
Anticholinergics		
Benztropine	Anticholinergic	8 (16.0%)

Note: Data were expressed as frequency (%).

Table 2 Clinician-Rated Dimensions of Patients' (N=50) Psychosis Symptom Severity (DSM-5)

Disorder	0	1	2	3	4	Score
Disorganized speech	16 (32.0%)	8 (16.0%)	12 (24.0%)	6 (12.0%)	8 (16.0%)	1.64±0.21 (0–4)
Cognitive impairment	15 (30.0%)	11 (22.0%)	17 (34.0%)	4 (8.0%)	3 (6.0%)	1.38±0.17 (0–4)
Negative symptoms	14 (28.0%)	18 (36.0%)	14 (28.0%)	1 (2.0%)	3 (6.0%)	1.22±0.15 (0–4)
Psychomotor activity abnormality	21 (42.0%)	12 (24.0%)	11 (22.0%)	5 (1.0%)	1 (2.0%)	1.06±0.16 (0–4)
Delusions	26 (52.0%)	9 (18.0%)	11 (22.0%)	4 (8.0%)	–	0.86±0.15 (0–3)
Hallucinations	27 (54.0%)	7 (14.0%)	16 (32.0%)	–	–	0.78±0.13 (0–2)
Mania	33 (66.0%)	11 (22.0%)	4 (8.0%)	1 (2.0%)	1 (2.0%)	0.52±0.13 (0–4)
Depression	41 (82.0%)	5 (10.0%)	4 (8.0%)	–	–	0.26±0.09 (0–2)
Score of clinically-related dimensions of psychosis symptom severity						8.02±0.70 (0–25)

Note: Data were expressed as frequency (%) or mean +/- standard error (minimum–maximum), as appropriate.

Complete Blood Count (CBC)

The CBC of patients and controls is shown in [Figure 1](#). In the current study, patients' $\text{LYM} \times 10^3/\mu\text{L}$, $\text{RBC} (\times 10^6/\mu\text{L})$, $\text{HGB} (\text{g/dL})$, $\text{HCT} (\%)$, $\text{MPV} (\text{fL})$ and $\text{PLT} (\times 10^3/\mu\text{L})$ were significantly decreased versus those of controls ($p=0.005$, $p=0.007$, $p=0.002$, $p=0.001$, $p=0.0001$ and $p=0.004$). Meanwhile, $\text{EOS} (\times 10^3/\mu\text{L})$, $\text{BASO} (\%)$ were significantly increased in patients versus controls ($p=0.009$, $p=0.0001$).

Liver Function Test (LFT)

The results of the liver function tests of patients and controls are shown in [Figure 2](#). Serum levels of albumin were significantly decreased in patients versus controls ($p=0.0001$).

C-Reactive Protein (CRP), Vitamin B12, and Folic Acid Levels

Serum levels of CRP were significantly increased in patients versus controls ($p=0.003$). Vitamin B12 levels were slightly lower in psychotic patients when compared to healthy controls. However, there was no statistical significance ($p=0.103$). There were insignificant changes regarding folic acid levels between patients and controls ($p=0.761$) ([Figure 3](#)).

Correlations Between Serum Levels of Vitamin B12 and Clinician-Rated Dimensions of Psychosis Symptom Severity (DSM-5)

There were significant negative correlations between serum levels of vitamin B12 and negative symptoms ($r=-0.381$, $p=0.006$) and hallucinations ($r=-0.297$, $p=0.036$). Meanwhile, there were no significant correlations between other components of DSM-5 and serum levels of vitamin B12 ([Figure 4](#)).

Discussion

This study was designed to determine the association between megaloblastic anemia due to vitamin B12 deficiency and psychosis among psychotic patients in the Mental Health Hospital at Taif. The study findings show no association between MA induced by Vitamin B12 insufficiency and psychosis among psychotic patients. Dogan et al reported a case of psychotic patients who showed a deficient vitamin B12 level with no signs of MA.²³ Payinda and Hansen published a case report of a 52-year-old patient diagnosed with psychosis and low serum vitamin B12 level without signs of anemia.²⁴ Rajkumar and Jebaraj reported a case of a 31-year-old man who suffered from psychotic symptoms with deficient vitamin B12 and no anemia.²⁵ Additionally, Ssonko et al published a study paper that included 280 inpatients at Mental Health Hospital in Uganda and they found that the majority of hospitalized psychiatric patients had deficient

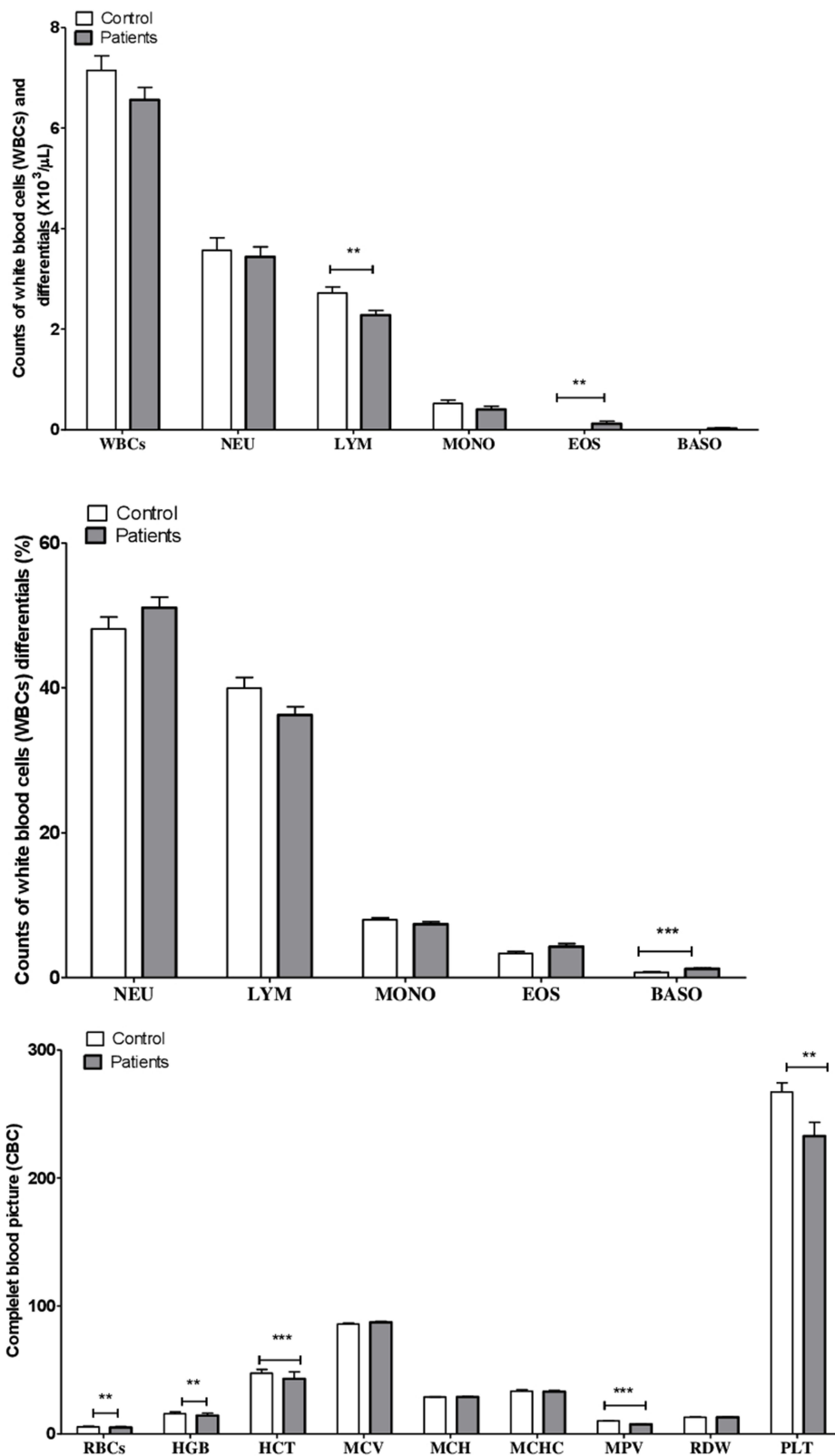


Figure 1 Complete blood count (CBC) in patients and controls. Data are expressed as mean +/- standard mean error. **P <0.010; ***P <0.001.

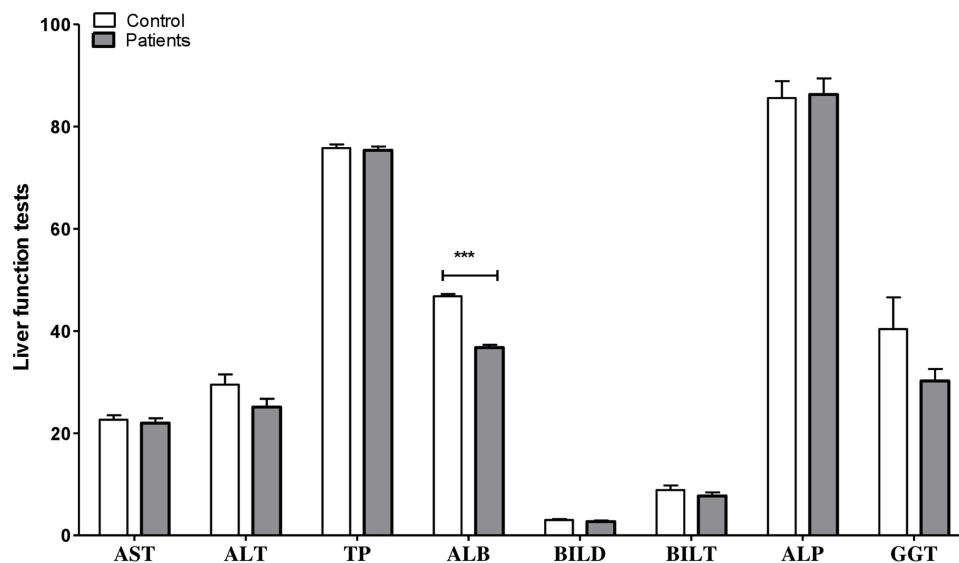


Figure 2 Liver function tests of patients and controls. Data are expressed as mean \pm standard mean error. *** $P < 0.001$.

serum vitamin B12 with no haematological finding of MA.²⁶ Lindenbaum et al performed on 141 patients at Harlem Hospital Centre and Columbia-Presbyterian Medical Center suffering from neuropsychiatric abnormalities caused by deficient vitamin B12. They conclude that neuropsychiatric disorders caused by low vitamin B12 occur commonly without anemia or abnormal elevated MCV.²⁷ The current study finding shows that psychosis inpatients have an insignificant lower serum vitamin B12 level when compared to controls. In addition, the study findings show a significant negative correlation between the serum level of vitamin B12 and the severity of two symptoms of psychosis: hallucinations and negative symptoms. Consequently, vitamin B12 levels can predict the severity of some psychosis signs, including hallucinations and negative symptoms. Sabeen and Holroyd published a paper concluding that low to moderately normal levels of vitamin B12 can cause psychiatric symptoms.²⁸ Lachner et al reported that establishing the normal serum vitamin B12 threshold range depends on population statistics. Active disease due to vitamin B12 deficiency may present, although the normal range of the metabolic requirements of individuals may vary. Another cause of a false negative result of the deficiency is that inactive Cbl form might be detected by radioimmunoassay and mimic the tissue deficiency of the active cobalamin. In addition, the concentration of vitamin B12 binding proteins may alter vitamin B12 level, causing a false negative result.²⁹ Another cross-sectional study among schizophrenic patients, by Hussein et al, found a significant negative correlation between vitamin B12 level and negative symptoms.³⁰ Engelborghs et al reported statistically significant negative correlations among frontotemporal dementia patients between hallucinations, levels of vitamin B12, and diurnal rhythm disturbances.³¹ Psychotic inpatients in current study are on antipsychotic drugs, antidepressants, anticonvulsants, and benzodiazepines to control their psychiatric symptoms, which might affect some laboratory results.

Neuronal demyelination, which affects both the peripheral and central nervous systems, is another traditional pathophysiological symptom of B12 insufficiency in addition to megaloblastic anemia. S-adenosylmethionine (SAM) shortage and subsequent suppression of methylation processes, which are necessary for membrane phospholipid metabolism and neurotransmitter metabolism, are one of the ideas behind demyelinating disease B12 deficiency-related myeloneuropathy possibly being brought on by a disruption in the metabolism of odd-chain fatty acids due to the suppression of the conversion of methylmalonyl CoA to succinyl CoA. B12 therapy corrects changes in cytokines and epidermal growth factor in cerebrospinal fluid and serum, which are linked to neurological symptoms of B12 deficiency in humans and rats and have been hypothesised to contribute to neuropathy.³

The only vitamin in the human body that contains cobalt is vitamin B12, which serves as a cofactor for enzyme methionine synthetase. Vitamin B12 deficiency is linked to a variety of neurologic, psychiatric, and neuropsychiatric disorders, including neuropathy, myelopathy, optic atrophy, cerebellar ataxia, and cognitive disorders like dementia,

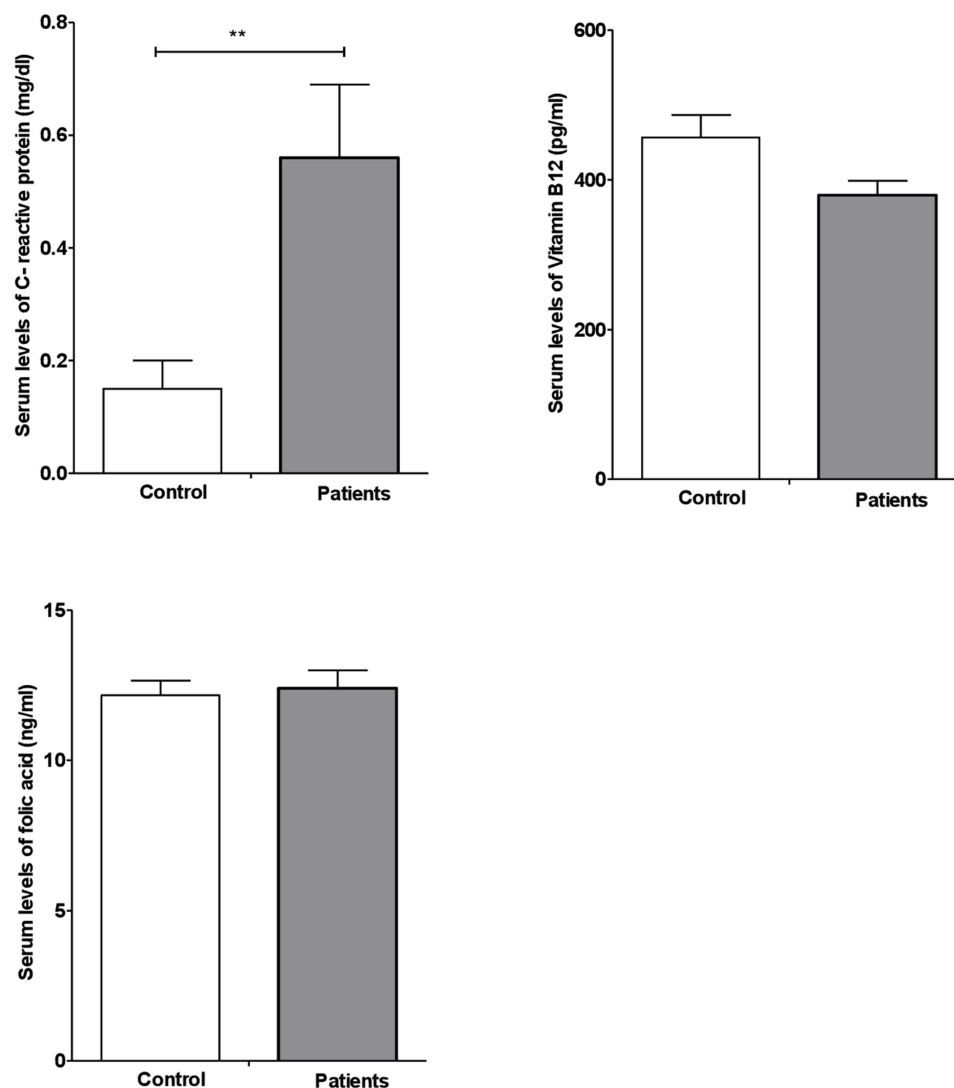


Figure 3 CRP, vitamin B12 and folic acid serum levels of patients and controls. Data are expressed as mean \pm standard mean error. ****** $P < 0.010$.

psychosis, and mood disorders.³² DNA and other molecules must be synthesised from nucleotides, which requires one-carbon metabolism (OCM). This cycle is a complex system that transfers a methyl group between several different conformations.³² Impaired folic acid and vitamin B12 levels are the main contributors to OCM changes.³³

The present study findings show significantly elevated CRP level within the schizophrenia inpatient group consistent with a published study by Dickerson et al among schizophrenic patients. In Dickerson et al's study, schizophrenia patients received the following medications: atypical antipsychotics (clozapine, risperidone, olanzapine), antidepressant medication, anti-cholinergic, and lithium.³⁴ In addition, a retrospective study by Hefner et al among patients treated with antipsychotics including clozapine and risperidone shows a significant correlation between the percentage increase in serum concentration of clozapine and risperidone and the serum level of CRP.³⁵ In the current study, CBC results show significant lymphocytopenia compared to the control subject. Moreover, psychosis inpatients show lower total WBC counts and neutrophil counts without statistical significance. Several case studies show that lymphocytopenia and neutropenia can be induced by combined risperidone and paliperidone treatment.^{36–39} Abanmy et al conducted a retrospective study in Saudi Arabia to report the incidence of clozapine-induced hematological toxicity. They reported that clozapine induces lymphocytopenia in 12.9% of their patients.⁴⁰ Psychotic inpatients in the current study also have significantly elevated eosinophil count and basophil percentages compared to control subjects. Several case studies

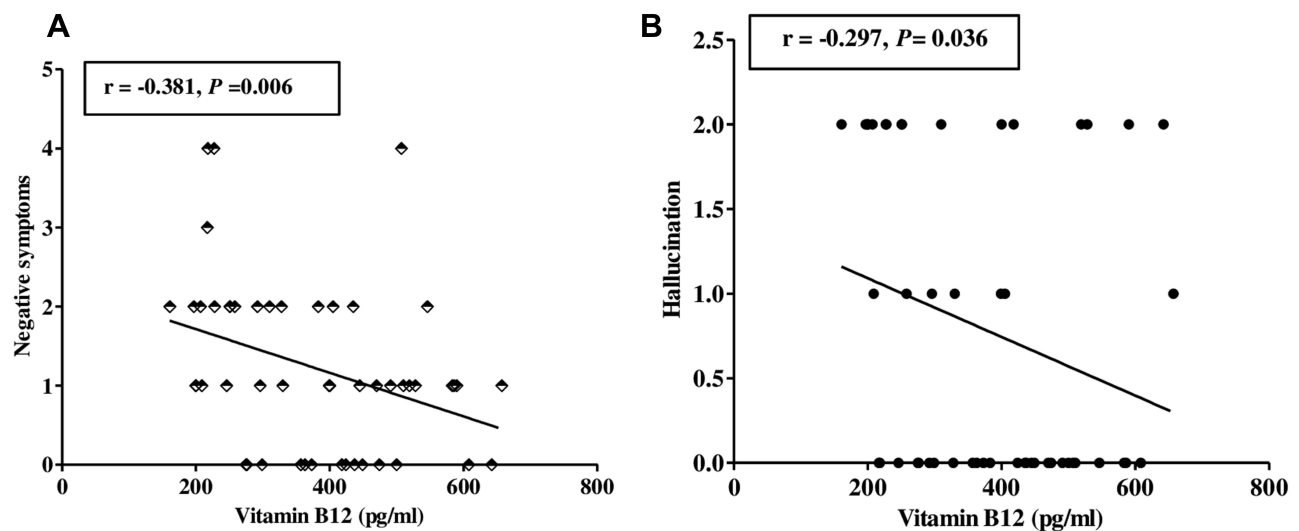


Figure 4 Correlations between patients' (N=50) serum levels of vitamin B12 and negative symptoms (A) and hallucinations (B).

reported that olanzapine^{41–43} and valproate induce eosinophil.⁴⁴ Tsamakidis et al published a paper concluding that elevated eosinophil count might be associated with antipsychotics. In their study, elevated eosinophil count was noted in psychiatric patients treated with haloperidol, olanzapine, and aripiprazole.⁴⁵ Lee et al reported a transient increase in basophil count after the first week of clozapine treatment.⁴⁶ RBC count, HBG, HCT, platelet count, and MPV were significantly lower in the patient group than in controls, which is consistent with a cross-sectional study conducted by Jombo and Ekwere on 60 persons with schizophrenia treated with either typical or atypical antipsychotics except for MPV. In contrast, their study findings show significantly higher RBCS count, Hb, Hct, platelet count, and MPV in patients than in controls.⁴⁷ Nasreddine and Beydoun indicate a negative correlation between valproate plasma level and platelet count.⁴⁸ The current study's findings show a significant decrease in the MPV of patients compared to controls. A study conducted by Ataoglu and Canan showed that patient platelet count and MPV results were significantly decreased following treatment with escitalopram.¹⁷ The liver function test finding of the current study showed a significant decrease in serum albumin level in inpatients. This agreed with the results of Zhai et al, which found a significant decrease in albumin following antipsychotic treatments.⁴⁹ In addition, a study conducted by Garcia-Unzueta et al found that serum albumin was significantly lower in schizophrenic patients under antipsychotic treatment compared to healthy controls.⁵⁰

Limitations

This study has some limitations. First, this is a case control study with a small sample size. Absence of data relating to duration of first-episode psychosis in psychotic patients is another limitation. Another limitation is that it was conducted in a single institution in Saudi Arabia and involved the male gender only, so the results obtained cannot be generalized.

Conclusions

This study was conducted to determine the association between megaloblastic anemia caused by vitamin B12 insufficiency and psychosis among psychotic patients in Mental Health Hospital in Taif. We aimed to find a causal relationship between MA and psychosis. Our study found no association between megaloblastic anemia and psychosis among psychotic patients in the Mental Health Hospital at Taif. However, psychotic inpatients had a low to moderate average vitamin B12 level, which might contribute to the psychosis symptoms. We found a significant negative correlation between the serum level of vitamin B12 and the severity of two symptoms of psychosis: hallucinations and negative

symptoms. According to our study findings, monitoring VitB12 levels in psychotic patients is recommended to improve their symptoms.

For future studies, we recommend recording baseline vitamin levels and assessing psychosis symptom severity at admission, and then following patients' symptoms after introducing vitamin B12 supplements. Moreover, increasing sample size and involving females in the study may obtain more accurate and precise results.

Data Sharing Statement

The data available are in the manuscript.

Institutional Review Board Statement

The study was approved by Taif Ethics Research Committee with approval number (471-2021). The study was executed in consensus with the guidelines followed by both Mental Health Hospital and King Faisal Medical Complex, Taif, Saudi Arabia, which were in accordance with Ministry of Health in Saudi Arabia.

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Disclosure

The authors declare that they have no competing interests.

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