# Original Article

# Unrecognized Prevalence of Macrocytosis among the Patients with First Episode of Psychosis and Depression

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## ABSTRACT

**Background:** Mood disorders and psychosis has been reported among the patients with macrocytosis; however, its prevalence among the first episode of psychosis and depression is unknown. The purpose of the study was to establish the prevalence of macrocytosis among the patients with the first episode of depression and psychosis. **Materials and Methods:** In this cross-sectional study, three groups comprising patients with first episode of depression ($n = 100$), patients with the first episode of psychosis ($n = 100$), and healthy controls ($n = 100$) were included. Blood samples were collected from each participant and analyzed using the automated coulter counter. The hematological variables (e.g., macrocytosis, anemia) in the three groups were compared using the Chi-square and analysis of variance tests. **Results:** The prevalence of macrocytosis among patients with depression and psychosis was 2.6 (8%) and 3.3 times (11%) higher, respectively than that among the healthy controls (3%). In addition, the hemoglobin concentration, mean corpuscular volume and mean platelet volume in patients with first episodes of psychosis and depression significantly differed from those in healthy controls $P < 0.001$. **Conclusion:** This study showed that the prevalence of macrocytosis among the first episode of depression and psychosis was higher than healthy controls. Macrocytosis may have etiological and prognostic significance among these patients. Prospective studies are needed to explore the clinical significance of macrocytosis among the patients with depression and psychosis in the clinical practice.

**Key words:** *Anemia, depression, macrocytosis, platelet count, psychosis*

## INTRODUCTION

Psychosis is a poorly understood condition, with a prevalence of 31.6 per 100,000 and includes affective and nonaffective subtypes.[1] Depression, by contrast, affects approximately 8%–12% of the general population and is the fourth leading cause of disability worldwide.[2] The biological bases of psychosis and depression have been postulated, but they remain poorly defined. Recent studies support the possibility

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of common etiological factors, such as the deficiency of Vitamin B12, folic acid, iron, and hypothyroidism as well as common immunological abnormalities such as altered growth factors and cytokines, underlying the two conditions.[3,4] In addition, these etiological factors have a vital role in predicting the clinical outcome of these conditions.[5-7] Moreover, patients with these etiologies are at an increased risk of cardiovascular diseases, obesity, and smoking as well as psychiatric comorbidities such as recurrent depressive disorder and bipolar affective disorder.[8,9]

Interestingly, the aforementioned factors directly or indirectly affect the hematological parameters, including white blood cell (WBC) count, mean platelet volume (MPV), and mean corpuscular volume (MCV).[10,11] For example, patients with psychosis and depression show increased platelet activity and an increased WBC count[12,13] and depression, psychosis occurs in patients with macrocytosis.[14] Early identification of macrocytosis may help the clinician to treat these etiological and prognostic factors promptly and efficiently. However, the prevalence of macrocytosis is still unknown among these commonly encountered clinical conditions. Complete blood count (CBC) is extensively studied, and it is a commonly advised test, which is performed to evaluate the composition and concentration of the cellular components of blood.[15] It assesses a practical indicator of various infections, anemia, dehydration, malnutrition, and immunological response.

Therefore, in the present study, we primarily assessed the prevalence of macrocytosis among the patients with the first episode of psychosis and depression. We also examined the prevalence of hematological abnormalities, namely, anemia, thrombocytosis, and compared hematological parameters among the patients with the first episode of psychosis and depression.

## MATERIALS AND METHODS

The cross-sectional study was carried out at a tertiary care teaching hospital in the Konkan region of Maharashtra. It was approved by the Institutional Ethical Committee of Rural Medical College. The study was conducted between August 2015 and January 2016 (6 months). Our study included drug naïve patients with first episode of psychosis (*n* = 100) or depression (*n* = 100) diagnosed by a psychiatrist, according to the International Classification of Diseases, 10th Revision criteria, aged between 18 and 45 years. The patients were recruited from outpatient services of psychiatry department. The control data were obtained from the caregivers of patients attending outpatient services of psychiatry

department and without any apparent psychiatric illness on an interview. The control group (*n* = 100) was selected to match the patients in terms of age and gender. The exclusion criteria for both patients and controls were a history of substance use, psychotropic medication, and micronutrient supplementation, as well as history of hepatic or renal failure, acute infection, leukemia, and aplastic anemia. Informed consent in the local language (Marathi) was obtained from all the participants after a detailed explanation of the nature of the study. The patients were assessed for dietary habits and Kuppuswamy socioeconomic scale (updated).[16] Five milliliters of blood was drawn from each participant into a bulb containing 0.04 mL of 7.5% ethylenediaminetetraacetic acid and analyzed using the automated coulter counter, within 2 h of collection. Five hematological parameters, namely, hemoglobin (Hb) concentration, WBC count, platelet count, MCV, and MPV were measured.

Statistical Package for Social Sciences software (SPSS 20.0, Chicago, IL, USA) was used for analysis. Descriptive parameters were shown as mean ± standard deviation or in percentages. Two-tailed *t*-tests and Pearson's Chi-square tests were used to analyze the differences in the means and proportions between groups, respectively. The analysis of variance test was used to compare more than two unmatched groups. Tukey's multiple comparisons test was used to compare the subgroups. $P < 0.05$ was considered statistically significant.

## RESULTS

The sociodemographic and clinical characteristics are provided in Table 1. The study comprised three age- and sex-matched groups, namely, patients with the first episode of depression (*n* = 100), patients with first episode of psychosis (*n* = 100), and healthy controls (*n* = 100). The Hb concentration, MCV, MPV was significantly higher in patients with first episodes of depression and psychosis than in the healthy controls; however, the WBC and platelet counts did not differ significantly between patients and healthy controls. In addition, there was no significant difference in terms of socioeconomic status and diet [Table 1].

Subgroup analyses were conducted using Tukey's multiple comparisons test [Table 2], which showed no significant differences in the WBC and platelet counts between the healthy controls and case groups. However, the differences in the MPV and Hb concentrations were highly significant between patients with psychosis and controls. The MCV of the patients with psychosis was significantly higher than that of the controls. Moreover, MCV and MPV

**Table 1: Sociodemographic and clinical characteristics**

| Variables | First episode of depression (*n*=100) | First episode of psychosis (*n*=100) | Healthy control (*n*=100) | Level of significance |
|---|---|---|---|---|
| Age (years) | 32.25±10.05 | 29.73±10.52 | 32.96±8.74 | $F_{(2, 297)}$=3.00, *P*=0.051[a] |
| Sex (%) | | | | |
| Male | 50 (50.00) | 46 (46.00) | 43 (43.00) | $\chi^2$=0.99; df=2, *P*=0.60[b] |
| Female | 50 (50.00) | 54 (54.00) | 57 (57.00) | |
| Diet (%) | | | | |
| Vegetarian | 24 (24.00) | 28 (28.00) | 20 (20.00) | $\chi^2$=1.75, df=2, *P*=0.41[b] |
| Mixed (vegetarian + nonvegetarian) | 76 (76.00) | 72 (72.00) | 80 (80.00) | |
| Kuppuswamy socioeconomic status scale updated[16] (%) | | | | |
| Lower class and upper lower class | 18 (18.00) | 17 (17.00) | 13 (13.00) | $\chi^2$=2.081, df=4, *P*=0.72[b] |
| Lower middle class | 70 (70.00) | 74 (74.00) | 73 (73.00) | |
| Upper class and upper middle class | 12 (12.00) | 9 (9.00) | 14 (14.00) | |
| Blood parameters | | | | |
| Hb concentration (g/dL) | 12.69±1.69 | 12.26±1.96 | 11.33±2.17 | $F_{(2, 297)}$=19.94, *P*<0.0001[a] |
| WBC count (counts/L) | 7.89±1.97 | 8.58±2.80 | 8.29±3.66 | $F_{(2, 297)}$=1.43, *P*=0.16[a] |
| Platelet count (×10³/μL) | 286.8±83.67 | 282.7±90.27 | 259.0±93.55 | $F_{(2, 297)}$=2.82, *P*>0.05[a] |
| MCV (fL) | 86.57±9.43 | 89.17±10.52 | 82.67±9.45 | $F_{(2, 297)}$=11.11, *P*<0.0001[a] |
| MPV | 7.13±0.87 | 7.17±0.98 | 6.80±0.83 | $F_{(2, 297)}$=5.14, *P*<0.001[a] |

[a]One-way ANOVA test; [b]Chi-square test. Hb – Hemoglobin; WBC – White blood cell; MCV – Mean corpuscular volume; MPV – Mean platelet volume; ANOVA – Analysis of variance

**Table 2: Multiple comparisons among the three studied groups (first episode of depression, first episode of psychosis, and healthy control)**

| Variables | Groups | Mean difference | *q* | 95% CI of difference |
|---|---|---|---|---|
| Hb concentration (g/dL) | Depression versus psychosis | 0.43 | 2.22 | −0.22-1.08 |
| | Depression versus control | 1.36 | 6.97*** | 0.70-2.01 |
| | Psychosis versus control | 0.93 | 4.75** | 0.27-1.58 |
| WBC count (counts/L) | Depression versus psychosis | −0.68 | 2.46 | −1.61-0.25 |
| | Depression versus control | −0.40 | 1.43 | −1.33-0.53 |
| | Psychosis versus control | 0.28 | 1.02 | −0.64-1.22 |
| MCV (fL) | Depression versus psychosis | −2.60 | 2.65 | −5.89-0.68 |
| | Depression versus control | 3.89 | 3.97* | 0.60-7.19 |
| | Psychosis versus control | 6.50 | 6.62*** | 3.21-9.79 |
| Platelet count (×10³/μL) | Depression versus psychosis | 4.19 | 0.47 | −25.74-34.12 |
| | Depression versus control | 27.81 | 3.12 | −2.12-57.74 |
| | Psychosis versus control | 23.62 | 2.64 | −6.31-53.55 |
| MPV | Depression versus psychosis | −0.03 | 0.35 | −0.31-0.26 |
| | Depression versus control | 0.33 | 3.86* | 0.04-0.61 |
| | Psychosis versus control | 0.36 | 4.22** | 0.073-0.64 |

Significance level: *Significant (*P*<0.05); **Highly significant (*P*<0.01); ***Very highly significant (*P*<0.001). CI – Confidence interval; Hb – Hemoglobin; WBC – White blood cell; MCV – Mean corpuscular volume; MPV – Mean platelet volume

of the patients with depression were also significantly higher than those of the control group. The difference in Hb concentration between the depression and control groups was highly significant. Interestingly, in our study, there was no significant difference among the other studied hematological indices between the two groups.

Table 3 depicts the prevalence of anemia among the three groups. Among the male patients with psychosis and depression, the prevalence of mild anemia was relatively higher than that among the healthy controls. In addition, a few patients with psychosis (6.52%) showed moderate anemia. The condition was relatively

poor among the female patients. The prevalence of all grades of anemia (mild, moderate, and severe) in patients with psychosis and depression was significantly higher than in healthy controls.

Table 4 shows that macrocytosis was significantly higher among the patients with psychosis than in patients with depression and healthy controls. Although microcytosis was more common among patients with depression than in those with psychosis, it is still comparable to that in healthy controls. There was no significant difference among the three groups in terms of WBC and platelet counts.

**Table 3: Prevalence of anemia among males and females**

| Hb concentration and degree of anemia | First episode of depression (n=100) (%) | First episode of psychosis (n=100) (%) | Healthy controls (n=100) (%) | Chi-square test, P |
|---|---|---|---|---|
| Males (g/dL) | | | | |
| Normal (>13) | 38 (76.00) | 30 (65.21) | 37 (86.04) | $\chi^2$=9.83, df=4, P=0.04 |
| Mild anemia (11-12.9) | 12 (24.00) | 13 (28.26) | 6 (14.48) | |
| Moderate anemia (8.0-10.9) | 0 | 3 (6.52) | 0 | |
| Severe anemia (<8) | 0 | 0 | 0 | |
| Total (n) | 50 | 46 | 43 | |
| Females (g/dL) | | | | |
| Normal (>12) | 16 (32.00) | 38 (70.37) | 45 (78.94) | $\chi^2$=31.66, df=6, P=<0.001 |
| Mild anemia (11-11.9) | 14 (28.00) | 8 (14.81) | 6 (10.52) | |
| Moderate anemia (8.0-10.9) | 20 (40.00) | 8 (14.81) | 5 (8.77) | |
| Severe anemia (<8) | 0 | 2 (3.70) | 2 (3.50) | |
| Total (n) | 50 | 54 | 57 | |

Hb – Hemoglobin

**Table 4: Distribution of the study groups based on mean corpuscular volume, white blood cell count, and platelet count**

| Variables | First episode of depression (n=100) (%) | First episode of psychosis (n=100) (%) | Healthy controls (n=100) (%) | $\chi^2$, df, P (level of significance) |
|---|---|---|---|---|
| MCV (fL) | | | | |
| Microcytosis (<80) | 24 (24.00) | 16 (16.00) | 33 (33.00) | $\chi^2$=10.99, df=4, P=0.02 |
| Normal (80-100) | 68 (68.00) | 73 (73.00) | 64 (64.00) | |
| Macrocytosis (>100) | 8 (8.00) | 11 (11.00) | 3 (3.00) | |
| WBC count (counts/L) | | | | |
| Leukopenia (4000) | 2 (2.00) | 2 (2.00) | 1 (1.00) | $\chi^2$=4.98, df=4; P=0.28 |
| Normal (4000-11,000) | 94 (94.00) | 87 (87.00) | 87 (87.00) | |
| Leukocytosis (>11,000) | 4 (4.00) | 11 (11.00) | 12 (12.00) | |
| Platelet count ($\times 10^3$/μL) | | | | |
| Thrombocytopenia (<150,000) | 2 (2.00) | 5 (5.00) | 7 (7.00) | $\chi^2$=3.86, df=4; P=0.42 |
| Normal (150,000-450,000) | 94 (94.00) | 91 (91.00) | 86 (86.00) | |
| Thrombocytosis (>450,000) | 6 (6.00) | 4 (4.00) | 7 (7.00) | |

WBC – White blood cell; MCV – Mean corpuscular volume

## DISCUSSION

In the present study, the prevalence of macrocytosis was higher among the patients with first episode of psychosis (11%) and depression (8%) than in healthy controls (3%). The prevalence of macrocytosis among the healthy controls is nearly in accordance with previously conducted studies among the general population (1.7%–3.6%).[17,18] The increased prevalence among these patients may suggest Vitamin B12 and folate deficiency, nonalcoholic liver diseases, hypothyroidism, and multiple myeloma, which often remain undiagnosed among the patients with these conditions.[19,20] Vitamin B12 and folic acid deficiencies contribute to the pathogenesis of neuropsychiatric disorders, such as mood disorder, mental confusion, memory changes, cognitive decline, and violent behavior, because of structural damage to the brain characterized by brain atrophy and silent brain infarct through multiple pathways.[21-23] Therefore, if interpreted carefully, macrocytosis may be a useful marker for patients with first episode of psychosis or depression in routine practice. The MCV is neither a specific nor a sensitive indicator of Vitamin B12 and folic acid deficiency;[24,25] however, it is a reasonable indicator of the Vitamin B12 deficiency, folic acid levels (blood), hypothyroidism, and immunological abnormalities which are common among the patients with depression and psychosis.[25]

In the present study, we observed an increased mean Hb concentration despite the presence of mild to moderate anemia and normal Hb level among the patients, which is extremely common in the Indian subcontinent.[26] It suggests the possibility of dimorphic anemia, i.e., deficiency of Vitamin B12, folic acid, and iron in the same individual. Iron deficiency causes microcytosis, whereas Vitamin B12 and folic acid deficiencies cause macrocytosis. A combined deficiency produces dimorphic anemia with a normal MCV level. Thus, several patients in our study may have shown a combined deficiency and may have, therefore, remained undiagnosed.[27] Higher MCV in the patients with first episodes of psychosis (89.17 ± 10.52 fL) and

depression (86.57 ± 9.43 fL) than in the healthy control group (82.67 ± 9.45 fL) provides further evidence supporting dimorphic anemia. The high MCV, which is associated with behavioral abnormalities, often remains undiagnosed, untreated, and overlooked by clinicians. A prospective study investigating serum Vitamin B12, folic acid, ferritin, and iron levels is warranted for more specific evaluation of anemia in patients with first episodes of depression and psychosis.

In this study, the overall mean Hb concentration was higher among the patients with psychosis and depression with a higher prevalence of mild to moderate anemia among females with first episode of depression than among males and healthy controls. The higher prevalence of depression among females may be secondary to anemia among them because iron deficiency is known to cause apathy, depression, and rapid fatigue.[28] Iron deficiency anemia begins in adolescence and becomes more pronounced among females of childbearing age. Therefore, females in this age group are at a higher risk of depression than are other patients. Another crucial reason for considering the Hb concentration is that maternal iron deficiency is associated with an increased risk of schizophrenia spectrum disorder among their offspring, through abnormal myelination and dopaminergic transmission.[29,30] Therefore, detecting anemia among females of childbearing age may facilitate in preventing the schizophrenia spectrum disorder and may enhance the quality of life by preventing cognitive decline.

Studies have established a distinct association between elevated WBC count, which is indicative of subclinical inflammation and immune changes, and depression and psychosis.[31,32] However, our study did not reveal an elevation in WBC count. The reason for this may be that the study included the first episode of illness, which may have been the pro-inflammatory state of an immunological event. Moreover, in contrast to previous studies, the present study included small number of participants and younger cohorts. The chronic cases included in previously conducted studies may have been in an inflammatory state because of the number of relapses (second hit) or the effect of various psychotropic medicines.

In index study, the MPV was higher in patients with either first episode of depression or psychosis than in the healthy controls with an insignificant increase in platelet count. The findings of the present study support those reported in previous studies indicating that patients with depression and psychosis exhibit increased platelet activation.[12,13] Platelet indices are considered vital mediators in the pathogenesis of cardiovascular diseases, metabolic syndrome, and inflammatory processes[33] as well as a significant peripheral marker of major psychiatric disorders, including depression and psychosis.[34,35] These findings are supportive of the inflammatory origin of depression and psychosis or may be indicative of an increased genetic vulnerability to future cardiovascular morbidities. Future studies exploring the use of the platelet indices in the CBC may be useful for assessing cardiovascular morbidity in patients with psychosis and depression.

### Strengths
The present study collectively interpreted and compared macrocytosis, the hematological parameters in patients with psychosis and depression, which is needed for every clinician in clinical practice. Previously conducted studies discretely investigated various nutritional deficiencies (Vitamin B12 and folic acid), iron deficiency, immunological abnormalities (WBC count), and risks of cardiovascular diseases (platelet count abnormalities) in patients with depression and psychosis. However, the present study findings will help the clinician to understand their vital role while interpreting CBC. The inclusion of only drug-naïve patients in our study can assist researchers to study the bidirectional association between etiology and illness. The present study findings such as anemia, macrocytosis among the patients may be due to nutritional problems secondary to social adversities in a rural area, and eventually, increase the risk for the occurrence of physical and emotional conditions.

### Limitations
The current study has few limitations; cross-sectional study design precludes the identification of direction of the association. Therefore, it is not possible to comment on the cause and effect of association between mental illness and blood parameters. However, these preliminary findings may help researchers to identify the probable role of poor dietary intake in mental illness including depression and psychosis. The estimation of serum B12, Folate levels and thyroid function tests with CBC will help to the clinician to explore common etiological factors and their prognostic significance among the patients with depression and psychosis in rural population.

## CONCLUSION

In the present study, higher prevalence of macrocytosis suggests that it is one of the unrecognized and undiagnosed in routine clinical practice. The prospective studies addressing the role of diseases (e.g., hypothyroidism, Vitamin B12, and folic acid deficiency) causing macrocytosis are needed to establish cause and effect relationship. In addition, treating these factors may help in prevention and treatment of psychosis and depression in future.

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**Conflicts of interest**

There are no conflicts of interest.

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