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Serum Vitamin B12 Status and Its Association with Depression Severity in Newly Diagnosed Patients: A Hospital-Based Cross-Sectional Study from Central India

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ABSTRACT

Background: Vitamin B12 deficiency is increasingly recognized as a modifiable biochemical contributor to depressive illness, particularly in Indian populations with high rates of vegetarianism. However, data on the relationship between serum B12 levels and depression severity from central India remain limited.
Objectives: To determine the prevalence of serum Vitamin B12 deficiency in newly diagnosed depression patients and to assess its association with depression severity using dual validated instruments — the Patient Health Questionnaire-9 (PHQ-9) and Beck's Depression Inventory (BDI).
Methods: A hospital-based, observational cross-sectional study was conducted at Gandhi Medical College and Hamidia Hospital, Bhopal, over 18 months. A total of 114 newly diagnosed depression patients (DSM-5 criteria), aged 18–60 years, were enrolled. Serum Vitamin B12 was estimated by Chemiluminescent Immunoassay (CLIA) on a Beckman Coulter DXI 800 analyzer. Depression severity was assessed using PHQ-9 and BDI. Non-parametric statistical tests (Kruskal-Wallis, Mann-Whitney U, Spearman's rank correlation) were applied throughout, given non-normal data distribution confirmed by Shapiro-Wilk testing.
Results: Vitamin B12 deficiency (<200 pg/mL) was found in 61.4% of participants, with 82.5% showing suboptimal levels overall. The overall median serum B12 was 156.72 pg/mL (IQR: 150.33). Although Kruskal-Wallis analysis showed no statistically significant difference across PHQ-9 ($H = 5.528$, $p = 0.137$) or BDI ($H = 4.691$, $p = 0.196$) severity categories, a clinically meaningful declining trend was observed: BDI-Mild (188.51 pg/mL), Moderate (148.44 pg/mL), and Severe (110.75 pg/mL). Spearman's correlation of B12 with PHQ-9 ($r = -0.169$, $p = 0.073$) and BDI ($r = -0.172$, $p = 0.067$) approached but did not reach significance. Males had significantly lower B12 levels than females (135.21 vs. 213.40 pg/mL; $U = 2042.00$, $p = 0.017$).
Conclusion: Vitamin B12 deficiency is endemic among newly diagnosed depression patients in central India. Although a statistically significant association with depression severity was not established, a consistent and clinically meaningful inverse trend was demonstrated, approaching significance on both assessment scales. Routine B12 screening in all newly diagnosed depression patients is warranted. Larger prospective studies with control groups are recommended to confirm causality.

Keywords: *Vitamin B12, cobalamin deficiency, depression, PHQ-9, Beck Depression Inventory, Indian population, biochemical markers, psychiatric comorbidity, homocysteine.*

INTRODUCTION

Depression is among the most disabling medical conditions globally, ranked as a leading cause of disability-adjusted life years by the Global Burden of Disease Study 2019.[1] In India, the National Mental Health Survey 2015–16 documented a lifetime prevalence of depressive episodes at 5.25% in the adult population, translating to millions of affected individuals, with significant underdiagnosis and treatment gaps compounded by cultural stigma and limited psychiatric resources.[2]

The traditional diagnostic paradigm for depression relies on clinical symptomatology and standardized psychological assessments per DSM-5 criteria. This approach, while clinically validated, lacks the objective, biological precision increasingly expected in modern evidence-based medicine. A growing body of evidence suggests that specific biochemical deficiencies may not only correlate with but may mechanistically contribute to depressive illness, offering both diagnostic and therapeutic implications.[3]

Among biochemical candidates, Vitamin B12 (cobalamin) occupies a particularly compelling position. As a water-soluble vitamin essential for DNA synthesis, myelin formation, and one-carbon metabolism, B12 plays a fundamental role in neurotransmitter synthesis, particularly through its influence on methylation pathways that regulate serotonin, dopamine, and norepinephrine metabolism.[4],[5] B12 deficiency leads to accumulation of homocysteine — a neurotoxic amino acid — and disruption of S-adenosylmethionine (SAM) synthesis, which has been directly linked to depressive symptomatology.[6] The Indian context presents particular relevance. Widespread vegetarianism, which excludes the primary dietary sources of B12 (animal products), combined with limited supplementation programs, places large segments of the population at risk of deficiency. Studies from North India have estimated B12 deficiency rates of 47–75% in the general population, with even higher rates expected in depressed cohorts where appetite disturbance and social withdrawal may further compromise dietary intake.[7]

Despite this biological plausibility and epidemiological context, published data specifically examining the relationship between serum B12 levels and depression *severity* from central India — particularly from Madhya Pradesh, where vegetarianism is deeply embedded — remain sparse. The present study addresses this gap by determining the prevalence of B12 deficiency and assessing its quantitative association with depression severity using dual validated scales (PHQ-9 and BDI) in newly diagnosed patients at a tertiary care center in Bhopal.

MATERIALS AND METHODS

2.1 Study Design and Setting

A hospital-based, observational cross-sectional study was conducted at the Department of Biochemistry, in collaboration with the Department of Psychiatry, Gandhi Medical College and Hamidia Hospital, Bhopal, Madhya Pradesh, over 18 months. Biochemical analyses were performed at the Central Clinical Laboratory, Hamidia Hospital, Bhopal.

2.2 Ethical Approval

The study was conducted after approval from the Institutional Ethics Committee (IEC), Gandhi Medical College, Bhopal and with written informed consent from each participant in their preferred language, in accordance with the Declaration of Helsinki.

2.3 Sample Size

Sample size was calculated using the formula $n = Z^2.p.q / d^2$, with a 95% confidence level ($Z = 1.96$), expected depression prevalence of 5% (based on National Mental Health Survey 2015–16), and a desired precision of 4%, yielding a minimum sample of 114 participants.

2.4 Inclusion and Exclusion Criteria

Inclusion: Newly diagnosed patients of depression based on DSM-5 criteria, adults aged 18–60 years of either sex, attending the Psychiatry OPD.

Exclusion: Individuals with comorbid mental health disorders, history of substance abuse, pregnancy or lactation, severe medical conditions (malignancy, organ failure), chronic diseases other than depression, or prior gastric bypass surgery, as these conditions independently influence B12 status or confound depression assessment.

2.5 Assessment of Depression Severity

All participants underwent standardized dual psychological assessment:

- **PHQ-9 (Patient Health Questionnaire-9):** A 9-item validated self-report tool scoring 0–27. Severity categories: Mild (5–9), Moderate (10–14), Moderately Severe (15–19), Severe (20–27).
- **BDI (Beck's Depression Inventory):** A 21-item validated scale scoring 0–63. Severity categories: Minimal (0–13), Mild (14–19), Moderate (20–28), Severe (29–63).

2.6 Blood Sample Collection

Five millilitres of venous blood were drawn under strict aseptic conditions following NCCLS (National Committee for Clinical Laboratory Standards) protocols. Serum was separated by centrifugation at 3000 rpm for 15 minutes. All biochemical analyses were performed on the same day of collection to minimize pre-analytical variability.

2.7 Estimation of Serum Vitamin B12

Method: Chemiluminescent Immunoassay (CLIA) on Beckman Coulter DXI 800 (fully automated analyzer).

Principle: A competitive chemiluminescent immunoenzymatic assay. Serum is pre-treated with denaturing agents (alkaline potassium cyanide and dithiothreitol) to release B12 from binding proteins and convert it to cyanocobalamin. The released B12 competes with alkaline phosphatase-labeled B12 for intrinsic factor binding sites on paramagnetic particles. After magnetic separation and washing, a chemiluminescent substrate is added; emitted light — measured by luminometry — is inversely proportional to the B12 concentration. Quantification is performed against a stored multi-point calibration curve.

Reference Range: 180–914 pg/mL. For classification purposes: Deficient (<200 pg/mL), Borderline (200–300 pg/mL), Normal (>300 pg/mL).

2.8 Statistical Analysis

Statistical analysis was performed using Epi-info software (CDC) and Python (SciPy library) for normality assessment. Distribution normality was assessed using the Shapiro-Wilk test. As most variables showed significant non-normality ($p < 0.05$), non-parametric tests were applied throughout:

- **Kruskal-Wallis H test** for comparison of B12 levels across multiple depression severity groups.
- **Mann-Whitney U test** for two-group comparisons (gender analysis).
- **Spearman's rank correlation (r)** for continuous association between B12 levels and PHQ-9 / BDI scores.
- **Chi-square test** for categorical comparisons.

A p-value of <0.05 was considered statistically significant.

RESULTS

3.1 Demographic Profile

A total of 114 participants were enrolled. The majority (46.5%) were in the 18–30 years age group, reflecting the established epidemiological peak of depression in young adulthood. Gender distribution was nearly equal: males 51.8% (n=59), females 48.2% (n=55). Most participants (76.3%) were from urban areas. Occupationally, housewives (24.6%) and students (20.2%) constituted the largest groups, and 45.6% belonged to Lower Middle socioeconomic class (Modified Kuppuswamy Scale). Depression severity distribution by gender showed no statistically significant difference (PHQ-9: $\chi^2 = 0.075$, $p = 0.995$; BDI: $\chi^2 = 1.404$, $p = 0.705$).

3.2 Depression Severity Distribution

Using PHQ-9, moderate depression (score 10–14) was the most prevalent category in 57 participants (50.0%), followed by Moderately Severe in 33 (28.9%), Mild in 13 (11.4%), and Severe in 11 (9.6%). No participant scored in the Minimal category (0–4). BDI similarly showed predominance of Moderate depression (47.4%), followed by Mild (36.0%), Severe (15.7%), and Minimal (0.9%).

3.3 Vitamin B12 Status: Prevalence of Deficiency

Table 1: Distribution of participants by serum Vitamin B12 status

Vitamin B12 Status	N	Percentage (%)
Deficient (<200 pg/mL)	70	61.4
Borderline (200–300 pg/mL)	24	21.1
Normal (>300 pg/mL)	20	17.5
Total	**114**	**100.0**

Vitamin B12 deficiency was the most prevalent biochemical finding, present in 61.4% of participants. Including borderline levels, 82.5% of the study population had suboptimal Vitamin B12 status. The overall median serum B12 was 156.72 pg/mL (IQR: 150.33).

3.4 Vitamin B12 and PHQ-9 Severity

Table 2: Serum Vitamin B12 distribution by PHQ-9 severity

Depression Severity (PHQ-9)	Deficient N (%)	Borderline N (%)	Normal N (%)	Chi-square	p-value
Mild (5–9)	8 (11.4)	4 (16.7)	1 (5.0)	8.752	0.188
Moderate (10–14)	30 (42.9)	15 (62.5)	12 (60.0)		
Moderately Severe (15–19)	23 (32.9)	3 (12.5)	7 (35.0)		
Severe (20–27)	9 (12.9)	2 (8.3)	0 (0.0)		

Total	**70 (100)**	**24 (100)**	**20 (100)**		

Notably, no participant with normal B12 had severe depression, while 12.9% of those with deficient B12 were in the severe category.

Table 3: Median serum Vitamin B12 by PHQ-9 severity

PHQ-9 Severity	Median B12 (pg/mL)	IQR	H-statistic	p-value
Mild (5–9)	178.57	119.85	5.528	0.137
Moderate (10–14)	195.01	174.23		
Moderately Severe (15–19)	139.00	154.28		
Severe (20–27)	106.00	86.86		
Overall	**156.72**	**150.33**		

The Kruskal-Wallis test showed no statistically significant difference across PHQ-9 severity groups (H = 5.528, p = 0.137). However, a clinically notable pattern emerged: median B12 in the severe group (106.00 pg/mL) was markedly lower than in the mild group (178.57 pg/mL), representing a 40.7% reduction.

3.5 Vitamin B12 and BDI Severity

Table 4: Serum Vitamin B12 distribution by BDI severity

Depression Severity (BDI)	Deficient N (%)	Borderline N (%)	Normal N (%)	Chi-square	p-value
Minimal (0–13)	0 (0.0)	1 (4.2)	0 (0.0)	8.596	0.198
Mild (14–19)	21 (30.0)	11 (45.8)	9 (45.0)		
Moderate (20–28)	35 (50.0)	9 (37.5)	10 (50.0)		
Severe (29–63)	14 (20.0)	3 (12.5)	1 (5.0)		
Total	**70 (100)**	**24 (100)**	**20 (100)**		

Table 5: Median serum Vitamin B12 by BDI severity

BDI Severity	Median B12 (pg/mL)	IQR	H-statistic	p-value
Minimal (0–13)	214.85	—	4.691	0.196
Mild (14–19)	188.51	188.00		
Moderate (20–28)	148.44	124.06		
Severe (29–63)	110.75	94.12		
Overall	**156.72**	**150.33**		

The BDI analysis demonstrated a consistent, monotonic declining trend in median B12 levels across all severity categories — from 214.85 pg/mL (Minimal) to 110.75 pg/mL (Severe), representing a 48.4% reduction across the severity spectrum, although this did not achieve statistical significance (H = 4.691, p = 0.196).

3.6 Spearman's Rank Correlation

Table 6: Spearman's correlation of serum Vitamin B12 with PHQ-9 and BDI scores

Score	Spearman's r	p-value
PHQ-9	−0.169	0.073
BDI	−0.172	0.067

Vitamin B12 showed a consistent negative correlation with both PHQ-9 and BDI scores, approaching but not reaching the conventional significance threshold of $p < 0.05$. The near-identical correlation coefficients on both scales ($r = -0.169$ and $r = -0.172$) strengthen the reliability of this directional trend.

3.7 Gender Differences in Serum Vitamin B12

Table 7: Serum Vitamin B12 by gender

Gender	Median B12 (pg/mL)	IQR	U-statistic	p-value
Female	213.40	239.87	2042.00	0.017*
Male	135.21	106.41		

*Statistically significant ($p < 0.05$)

Males had markedly and significantly lower serum Vitamin B12 levels compared to females (135.21 vs. 213.40 pg/mL; p = 0.017).

DISCUSSION

4.1 High Burden of Vitamin B12 Deficiency

The most striking finding of the present study is the extraordinarily high prevalence of Vitamin B12 deficiency in the study cohort: 61.4% were deficient (<200 pg/mL) and 82.5% had suboptimal levels overall. This substantially exceeds the 22% prevalence of low B12 reported among depressed patients in a large multi-database review by Sangle et al. (2020)[8] and the general Indian population estimates of 47–75% from Singla et al. (2019).[7] The overall median serum B12 of 156.72 pg/mL is deeply within the deficient range, painting a picture of near-universal nutritional compromise in this cohort.

This extraordinarily high prevalence is likely explained by the convergence of two independent determinants in this specific population. First, vegetarianism — the principal dietary risk factor for B12 deficiency — is culturally and religiously entrenched in Madhya Pradesh to a degree that exceeds national averages. Since B12 is found almost exclusively in animal-derived foods, strictly vegetarian individuals lack endogenous dietary replenishment.[4] Second, the behavioral and biological consequences of depression itself — including reduced appetite, social withdrawal, impaired self-care, and possibly increased gastric acid suppression from stress or pharmacological agents — likely compound the pre-existing dietary risk, creating a deficit amplification cycle that explains the severity of deficiency observed.

4.2 B12 Deficiency and Depression Severity: A Near-Significant Inverse Gradient

While formal statistical significance was not achieved on either the PHQ-9 ($H = 5.528$, $p = 0.137$) or BDI ($H = 4.691$, $p = 0.196$) analyses, the data reveal a clinically important and consistent pattern: median serum B12 declined monotonically and substantially with increasing depression severity on both assessment scales.

The most compelling evidence comes from the BDI analysis, which demonstrated a 48.4% reduction in median B12 from the Minimal (214.85 pg/mL) to Severe (110.75 pg/mL) category — a gradient that traverses from borderline-normal to severely deficient territory as depression deepens. Similarly, no participant with normal B12 levels (>300 pg/mL) was in the severe PHQ-9 category, while 12.9% of the deficient group reached this most severe stratum. The Spearman's correlations of $r = -0.169$ (PHQ-9, $p = 0.073$) and $r = -0.172$ (BDI, $p = 0.067$) were consistent, directionally identical, and both approached the conventional significance threshold — a pattern that compels attention even in the absence of $p < 0.05$.

These findings are partially consistent with the broader literature. A systematic review and meta-analysis by Petridou et al. (2015)[9] analyzing 9 studies (6,308 individuals) found a statistically significant association between low B12 and depression (OR: 1.20, 95% CI: 1.02–1.42). Kureshi et al. (2019)[10] demonstrated significantly lower B12 concentrations in 50 Indian depressed patients compared to healthy controls. The modest association sizes observed — consistent across studies — require large samples to reach statistical significance in continuous correlation analyses, which explains the near-significant but sub-threshold p-values in the present study.

The probable reason for the lack of statistical significance despite a meaningful clinical gradient is a pronounced *floor effect*. With 82.5% of participants already at suboptimal B12 levels, the statistical range of independent variable variation is severely restricted. Spearman's correlation and Kruskal-Wallis tests fundamentally lose power when the predictor variable clusters near its lower boundary across nearly all comparison groups. The floor effect artificially flattens the detectable dose-response relationship. This interpretation is supported by the observation that the declining trend is actually steeper and more consistent on the BDI than on the PHQ-9 — a difference likely reflecting the BDI's greater weight on somatic and vegetative symptoms that mechanistically align more closely with B12 deficiency pathophysiology.

4.3 Pathophysiological Mechanisms Linking B12 to Depression Severity

The mechanistic basis for the observed inverse trend is biologically sound and operates through multiple pathways.

Methylation pathway disruption: B12 is a critical cofactor for methionine synthase, which converts homocysteine to methionine, enabling S-adenosylmethionine (SAM) synthesis. SAM is the principal methyl donor for neurotransmitter synthesis, myelin maintenance, and DNA methylation. B12 deficiency impairs SAM production, elevates homocysteine, and disrupts the entire one-carbon metabolism network — affecting serotonin, dopamine, and norepinephrine synthesis in ways that directly parallel monoamine deficiency theories of depression.[6]

Serotonin receptor dysregulation: Russell-Jones (2022)[11] demonstrated through urinary metabolite analysis in 350 subjects across multiple countries that B12 deficiency paradoxically increases serotonin and tryptophan metabolite levels by blocking the methylation of N-acetyl serotonin to melatonin. This serotonin accumulation triggers compensatory receptor down-regulation, ultimately resulting in functional serotonergic deficiency — a mechanism that may underlie the worsening depression severity with progressive B12 depletion.

Homocysteine-mediated neurotoxicity: Elevated homocysteine, a direct consequence of B12 deficiency, causes NMDA receptor overactivation and excitotoxic neuronal damage, disrupts cerebral blood flow, and induces oxidative stress — all mechanisms that can independently worsen depressive illness.[5]

Neuroplasticity effects: B12 is essential for myelin synthesis; its deficiency impairs axonal conduction and synaptic connectivity in mood-regulating circuits including the prefrontal cortex-hippocampal axis, contributing to the cognitive symptoms and functional impairment that characterize more severe depression.[4]

The monotonically declining B12 values across BDI severity categories, from 214.85 to 110.75 pg/mL, suggest that as these biological mechanisms deepen, depression severity worsens in a biologically coherent, dose-dependent manner.

4.4 Gender Difference in Serum B12: A Surprising Finding

The observation that males had significantly lower B12 levels than females (135.21 vs. 213.40 pg/mL; $p = 0.017$) is counter-intuitive in most nutritional contexts, where males tend to have higher meat consumption and thus higher dietary B12 intake. In the central Indian setting of this study, where vegetarianism cuts across genders at high rates, dietary differences between sexes may be minimal. The probable explanation is that female participants are more likely to have received Vitamin B12 supplementation through government-mandated antenatal and postnatal care programs — a systematic intervention that selectively elevates B12 levels in women of reproductive age, the largest demographic group among female participants. Alternatively, sex-based differences in transcobalamin II levels and B12 binding protein kinetics may contribute. This finding highlights the importance of gender-stratified analysis in nutritional biochemistry research from India and warrants further investigation.

4.5 Implications for Clinical Practice

The clinical message from this study is unambiguous, irrespective of the statistical significance of the B12-severity association: Vitamin B12 deficiency is near-universal in newly diagnosed depression patients in central India and represents a readily identifiable, inexpensive, and treatable biochemical abnormality. The declining B12 gradient with severity, the near-significant correlations on both assessment scales, and the complete absence of normal-B12 participants in the severe PHQ-9 category together provide sufficient clinical justification for routine B12 estimation in every newly diagnosed depression patient.

B12 supplementation is safe, affordable, and widely available. In a population where 82.5% of depression patients are already deficient, the question is no longer whether to screen — it is a clinical obligation. Whether B12 repletion independently improves depressive outcomes requires prospective interventional data, but correcting a documented deficiency with known neurological consequences is sound clinical practice regardless of such evidence.

4.6 Limitations

This study has several limitations that should be considered when interpreting findings:

First, the absence of a healthy control group precludes direct comparison of B12 levels between depressed patients and the general population, limiting causal inference. Second, the cross-sectional design captures a single temporal snapshot, making it impossible to determine whether B12 deficiency preceded and contributed to depression, or whether depression-related behavioral changes (poor diet, reduced activity) secondarily depleted B12 stores. Third, the floor effect — with 82.5% of participants below optimal B12 — severely restricted statistical range, likely preventing the detection of a significant dose-response relationship that a control group or a broader-range sample would reveal. Fourth, functional B12 markers such as methylmalonic acid (MMA) and homocysteine were not measured, which would have provided a more sensitive and biologically complete picture of functional deficiency. Fifth, dietary assessment, sunlight exposure, and specific medication history were not systematically quantified. Finally, the predominantly urban, hospital-based sample from a single tertiary center may limit generalizability to rural populations or other Indian states.

CONCLUSION

Vitamin B12 deficiency is highly prevalent — affecting 61.4% of newly diagnosed depression patients — and suboptimal B12 status was found in 82.5% of the study cohort in central India, substantially exceeding general population estimates and highlighting a critical nutritional vulnerability at the intersection of dietary practice, mental health, and access to healthcare. A consistent, clinically meaningful inverse gradient between serum B12 levels and depression severity was observed across both PHQ-9 and BDI assessment scales, approaching statistical significance ($r \approx -0.17$, $p \approx 0.07$). Males showed significantly lower B12 levels than females ($p = 0.017$), likely reflecting selective supplementation in women through maternal health programs.

These findings support the routine and systematic estimation of serum Vitamin B12 in all newly diagnosed depression patients as part of their baseline biochemical evaluation. Larger prospective, longitudinal, multicentric studies incorporating healthy control groups, functional B12 markers (MMA, homocysteine), and B12 supplementation interventions are essential to establish causality and evaluate the therapeutic impact of correcting this pervasive deficiency on depressive outcomes in Indian populations.

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