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Original Article

Correlation of Folic Acid and Vitamin B12 With Red Cell Parameters in Suspected Cases of Oral Cancer

Afifa Fatima[1], Sehrish Zia[1], Shaista Emad[1], Rubina Ghani[1,2]

1 Department of Biochemistry, Jinnah Medical & Dental College/Sohail University, Karachi, Pakistan

[2] Pathological and Molecular Laboratories, Karachi, Pakistan

Correspondence: rubina.ghani@sohailuniversity.edu.pk
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ABSTRACT

Background: Oral cancer (OC) is a leading cause of cancer-related mortality in South Asia, with gutka, paan masala, betel nut, and tobacco consumption identified as major risk factors. Micronutrient deficiencies, particularly vitamin B12 and folic acid, may contribute to hematological abnormalities and increase susceptibility to oral carcinogenesis. However, their association with red blood cell (RBC) parameters in high-risk populations remains underexplored. Objective: To investigate the correlation between serum vitamin B12 and folic acid levels with hematological indices, particularly mean corpuscular volume (MCV), in individuals with suspected oral cancer who engage in high-risk chewing habits. Methods: A cross-sectional observational study was conducted among 96 participants from a peri-urban community near Karachi, Pakistan. Hematological parameters (hemoglobin, RBC count, hematocrit, MCV, MCH, MCHC, RDW, platelets, ESR) were assessed using an automated hematology analyzer, and serum vitamin B12 and folic acid were quantified via electrochemiluminescence immunoassay. Statistical analysis involved t-tests and Pearson's correlations (SPSS v25.0), with significance set at $p < 0.05$. Results: Mean MCV was elevated (96.2 ± 16.2 fL), with 45% and 32% of participants deficient in folic acid and vitamin B12, respectively. MCV correlated negatively with folic acid ($r = -0.82$, $p < 0.001$) and vitamin B12 ($r = -0.83$, $p < 0.001$). Participants with low vitamin levels exhibited significantly higher MCV and lower hemoglobin ($p < 0.05$). Conclusion: Deficiencies of vitamin B12 and folic acid are strongly associated with macrocytic changes in suspected OC cases, underscoring their role as early hematological markers for risk assessment.
Keywords: oral cancer, vitamin B12, folic acid, macrocytosis, red cell indices, gutka, paan masala.

INTRODUCTION

Oral cancer (OC) ranks among the leading causes of cancer-related morbidity and mortality worldwide and accounts for approximately 5% of all newly diagnosed malignancies (1). In Southeast Asia, particularly in Pakistan and India, the incidence of OC has risen alarmingly due to widespread cultural practices involving the use of smokeless tobacco products such as gutka, paan masala, and betel nuts (2). Globally, recent estimates indicate 354,864 new cases and 177,384 deaths annually, underscoring the severity of the disease burden (3). These statistics highlight the urgent need for early detection, improved preventive strategies, and effective diagnostic biomarkers to reduce the incidence and improve outcomes in high-risk populations.

OC development is strongly associated with lifestyle factors, particularly chronic consumption of gutka and paan masala, which are easily accessible, inexpensive, and socially accepted among various socioeconomic groups (4). Gutka and paan masala are complex mixtures containing areca nut, tobacco, slaked lime, catechu, and carcinogenic additives that contribute to genotoxicity, chromosomal aberrations, and epithelial tissue damage (5). Continuous exposure to these carcinogens induces molecular changes in oral mucosa, leading to potentially malignant disorders such as leukoplakia and oral submucous fibrosis, which can progress to oral squamous cell carcinoma (OSCC) (6). OSCC is the most prevalent form of OC, with prognosis heavily dependent on early detection and the extent of lymph node metastasis (7). Moreover, epidemiological studies have demonstrated that co-exposure to alcohol and poor dietary patterns further exacerbate the risk of OC (8).

Micronutrient deficiencies, particularly of vitamin B12 and folic acid, have been increasingly recognized as contributing factors in oral carcinogenesis. Vitamin B12 plays a critical role in DNA synthesis, methylation, and red blood cell formation, and its deficiency leads to macrocytic anemia characterized by elevated mean corpuscular volume (MCV) and the presence of macrocytes (9). Similarly, folic acid is essential for nucleotide biosynthesis and cellular repair mechanisms; its deficiency results in epithelial tissue lesions, impaired DNA repair, and genomic instability, which are conducive to neoplastic transformation (10). Several studies have indicated that folate depletion and low vitamin B12 status are prevalent among habitual tobacco and betel nut users, potentially due to impaired absorption or dietary

inadequacy (11). The interaction between nutritional deficiencies and carcinogen exposure could amplify the risk of OC, but this association remains underexplored in high-risk populations such as those in South Asia.

Previous investigations have explored hematological alterations as indirect markers of nutritional status and inflammation in cancer patients. Elevated MCV, anemia, and abnormal red cell distribution width (RDW) have been reported in OC and premalignant lesions, potentially serving as early warning signs (12). However, there is a paucity of studies that systematically correlate hematological indices with micronutrient status in populations with a high prevalence of gutka and paan masala use. While Gupta et al. (13) highlighted abnormal vitamin B12 levels in patients with oral malignancies, few studies have addressed the combined role of both vitamin B12 and folic acid in relation to red blood cell parameters in individuals with suspected OC in Pakistan.

Given the limited evidence from South Asian cohorts, there is a clear knowledge gap regarding the role of basic hematological and biochemical markers, such as vitamin B12, folic acid, and red blood cell indices, in identifying individuals at risk for OC. Early identification of these alterations could enable timely interventions, dietary modifications, and risk stratification for patients exposed to carcinogenic habits such as gutka, betel nut, and tobacco chewing. Therefore, this study aims to examine the correlation between folic acid and vitamin B12 levels with red blood cell parameters, particularly mean corpuscular volume (MCV), in suspected cases of oral cancer. We hypothesize that deficiencies of vitamin B12 and folic acid are significantly associated with macrocytosis and hematological abnormalities in individuals with high-risk habits, providing valuable insights for early detection and preventive strategies.

MATERIAL AND METHODS

This cross-sectional observational study was conducted to evaluate the correlation between serum folic acid, vitamin B12, and red blood cell (RBC) parameters among individuals with suspected oral cancer who reported long-term use of gutka, paan masala, betel nut, and tobacco-based products. The study was carried out between February and August 2024 in a peri-urban settlement near the Toll Plaza area of Karachi, Pakistan. The setting was selected due to the high prevalence of smokeless tobacco consumption in this population, allowing the recruitment of individuals at elevated risk for oral cancer.

Participants were recruited using a purposive sampling approach, targeting adults who self-reported daily consumption of gutka, paan masala, betel nut, or mawa since childhood. Eligible participants were individuals aged 14–65 years who exhibited clinical signs suggestive of oral precancerous conditions, including restricted mouth opening, fibrous bands in the buccal mucosa, oral lesions, or red and white mucosal patches. Exclusion criteria included a self-reported history of cardiovascular disease, metabolic syndrome, inflammatory bowel disease, hematological disorders, kidney or liver dysfunction, and malignancies other than oral cancer. Additionally, individuals on antiplatelet therapy or those who had discontinued gutka or tobacco-related habits for more than three years were excluded to avoid confounding effects of past exposures. Participants were informed about the study objectives, and written informed consent was obtained prior to enrollment, with parental consent required for individuals under 18 years of age.

A total of 96 participants were included in the study. Demographic and lifestyle data, including age, sex, substance use patterns, and dietary history, were collected through structured interviews conducted by trained research personnel. Blood samples were collected after an overnight fast. Approximately 4 mL of venous blood was drawn from each participant: 2 mL was collected in an EDTA tube for hematological analysis and 2 mL in a plain red-top tube for biochemical assays. Hematological parameters, including hemoglobin concentration, RBC count, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet count, and erythrocyte sedimentation rate (ESR), were measured using an automated hematology analyzer (Mindray BC-3000 Plus, Shenzhen, China) within two hours of sample collection. Serum vitamin B12 and folic acid concentrations were quantified by electrochemiluminescence immunoassay on a Cobas e402 analyzer (Roche Diagnostics, Germany), following manufacturer protocols. All assays were performed in duplicate to ensure precision, and calibration controls were run daily.

The primary variables were serum vitamin B12 (pg/mL) and folic acid (ng/mL) levels, while the main outcome measures were RBC parameters, particularly MCV as an indicator of macrocytosis. Macrocytic anemia was operationally defined as an MCV >100 fL, whereas low vitamin B12 and folic acid levels were defined based on laboratory reference ranges (vitamin B12 <200 pg/mL, folic acid <4 ng/mL). Potential confounding factors such as age, alcohol consumption, and combined tobacco product use were documented and analyzed to minimize bias. To address potential measurement bias, all laboratory procedures were conducted by a blinded technician, and duplicate sample runs were averaged for analysis. Sample size determination was based on prior studies examining correlations between hematological indices and micronutrient deficiencies in oral cancer risk groups, which suggested a moderate correlation ($r = 0.3–0.4$) with a statistical power of 80% and alpha of 0.05 (14,15). Using these parameters, the required sample size was calculated to be 85 participants, and we recruited 96 to account for potential missing data and variability. Data integrity was ensured by double-entry of data into a secure database and routine cross-checking of 10% of entries for accuracy.

Statistical analysis was conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) with 95% confidence intervals (CI). The normality of continuous data was assessed using the Shapiro-Wilk test. Pearson's correlation coefficients were calculated to evaluate the relationship between vitamin B12, folic acid, and RBC indices, with significance set at $p < 0.05$. Independent t-tests were performed to assess differences in hematological parameters between groups with normal versus low vitamin B12 and folate levels. Subgroup analyses were conducted based on patterns of substance use (gutka vs. betel nut vs. mixed habits). Missing data, which were minimal (<2%), were addressed using pairwise deletion. Ethical approval for this study was obtained from the Institutional Review Board of Sohail University/Jinnah Medical and Dental College, Karachi (Approval No. SU-BIO-2024-18). All procedures adhered to the ethical standards of the Helsinki Declaration. To ensure reproducibility, detailed standard

operating procedures were documented for all laboratory assays, and quality control protocols were implemented throughout data collection and analysis.

RESULTS

Of the 96 participants enrolled, substance use patterns demonstrated a heavy predominance of combined exposures. As shown in Table 1, 35% (n=34) of individuals reported concurrent use of gutka and mawa, with a 95% confidence interval (CI) from 25.1% to 45.9%. Approximately one-third, or 33% (n=32; 95% CI: 23.3%–43.7%), used a combination of betel nuts, paan masala, and gutka. Other patterns included betel nuts, gutka, paan masala, and hukka (18%, n=17), daily use of niswar and tobacco (7%, n=7), and a smaller group of participants (6.2%, n=6) reported alcohol consumption along with tobacco smoking and betel nut chewing. These overlapping habits highlight the complexity of exposure within this population.

Table 1. Prevalence of Substance Use in Study Population (N = 96)

Substance Use Pattern	n (%)	95% CI
Gutka and mawa	34 (35)	25.1 – 45.9
Betel nuts, paan masala, gutka	32 (33)	23.3 – 43.7
Alcohol, tobacco, betel nut	6 (6.2)	1.3 – 11.0
Betel nuts, gutka, paan masala, hukka	17 (18)	10.0 – 25.9
Niswar and tobacco chewed	7 (7)	2.0 – 13.1

Table 2. Baseline Hematological and Biochemical Parameters

Parameter	Mean ± SD	95% CI	Range
Age (years)	31.4 ± 13.0	26.9 – 35.9	14 – 65
Hemoglobin (g/dL)	11.2 ± 2.1	10.5 – 12.0	7.4 – 15.1
RBC count (×10⁶/µL)	4.32 ± 0.69	4.07 – 4.57	2.89 – 5.45
Hematocrit (%)	40.4 ± 6.2	38.2 – 42.6	27.9 – 53.7
MCV (fL)	96.2 ± 16.2	90.5 – 101.8	62.3 – 128.8
MCH (pg/cell)	26.2 ± 4.1	24.8 – 27.7	15.6 – 37.5
MCHC (g/dL)	28.0 ± 4.8	26.3 – 29.6	21.7 – 37.3
RDW (%)	20.1 ± 2.1	19.4 – 20.9	16.4 – 24.8
Platelet count (×10³/µL)	174.1 ± 58.4	153.8 – 194.5	89.0 – 330.0
ESR (mm/hr)	27.5 ± 6.3	25.3 – 29.7	15.0 – 45.0
Folic acid (ng/mL)	6.3 ± 6.4	4.1 – 8.6	0.39 – 18.0
Vitamin B12 (pg/mL)	312.5 ± 140.3	250.8 – 375.1	119 – 658

Table 3. Comparison of Hematological Indices by Vitamin B12 and Folic Acid Status

Parameter	Low B12 (n=31)	Normal B12 (n=65)	p-value	95% CI of Difference	Cohen's d
Hemoglobin (g/dL)	10.5 ± 2.3	11.7 ± 1.8	0.028	0.12 – 2.29	0.60
MCV (fL)	105.6 ± 13.4	91.5 ± 15.0	<0.001	8.42 – 20.41	1.00
RDW (%)	21.1 ± 2.1	19.7 ± 2.0	0.045	0.03 – 2.72	0.68
RBC count (×10⁶/µL)	3.98 ± 0.65	4.47 ± 0.64	0.011	0.13 – 0.86	0.76
Folic acid (ng/mL)	4.1 ± 3.2	7.5 ± 7.0	0.015	0.77 – 6.18	0.61

Similar comparisons for low vs. normal folic acid status are available upon request; results are directionally consistent.

Table 4. Correlation of Serum Folic Acid and Vitamin B12 with Hematological Parameters

Parameter	Folic Acid (r)	Folic Acid (p)	Vit B12 (r)	Vit B12 (p)	95% CI for r (Folic)	95% CI for r (B12)
MCV (fL)	-0.816	<0.001	-0.830	<0.001	-0.73, -0.90	-0.76, -0.90
RBC count (×10⁶/µL)	0.380	0.027	0.454	0.007	0.05, 0.65	0.17, 0.68
Hematocrit (%)	-0.523	0.002	-0.456	0.007	-0.70, -0.22	-0.66, -0.13
MCH (pg/cell)	-0.373	0.030	-0.476	0.004	-0.63, -0.03	-0.67, -0.16
MCHC (g/dL)	0.525	0.001	0.429	0.011	0.22, 0.70	0.12, 0.65
RDW (%)	-0.186	0.292	-0.199	0.258	-0.46, 0.13	-0.46, 0.11
Platelets (×10³/µL)	0.266	0.129	0.231	0.189	-0.10, 0.52	-0.13, 0.54
ESR (mm/hr)	-0.134	0.449	-0.126	0.479	-0.41, 0.19	-0.41, 0.17

All p-values two-sided; significance considered at $p < 0.05$.

Table 2 presents the baseline hematological and biochemical indices for the full cohort. The mean age was 31.4 years (SD 13.0, 95% CI: 26.9–35.9), with ages ranging from 14 to 65 years. Hemoglobin concentrations averaged 11.2 g/dL (SD 2.1, 95% CI: 10.5–12.0), notably lower than the reference range, indicating widespread anemia. Red blood cell (RBC) counts averaged 4.32 × 10⁶/µL (SD 0.69, 95% CI: 4.07–4.57). Hematocrit averaged 40.4% (SD 6.2, 95% CI: 38.2–42.6). The mean corpuscular volume (MCV) was elevated at 96.2 fL (SD 16.2, 95% CI: 90.5–101.8), with values spanning 62.3 to 128.8 fL, suggesting macrocytic tendencies in a substantial proportion of participants. MCH and MCHC also showed moderate variability, while RDW averaged 20.1% (SD 2.1), reflecting increased red cell size variation. Platelet counts ranged from 89,000 to 330,000/µL, with a mean of 174,100/µL (SD 58,400), and the mean ESR was 27.5 mm/hr

(SD 6.3, 95% CI: 25.3–29.7). Biochemically, the mean folic acid level was 6.3 ng/mL (SD 6.4, 95% CI: 4.1–8.6), and mean serum vitamin B12 was 312.5 pg/mL (SD 140.3, 95% CI: 250.8–375.1), with 45% and 32% of participants, respectively, falling below the reference ranges for these micronutrients.

When stratified by micronutrient status (Table 3), individuals with low vitamin B12 (<200 pg/mL, n=31) had a mean MCV of 105.6 fL (SD 13.4), significantly higher than those with normal vitamin B12 (91.5 fL, SD 15.0; $p < 0.001$, 95% CI of difference: 8.42–20.41). These individuals also had lower hemoglobin (10.5 g/dL vs 11.7 g/dL; $p = 0.028$, 95% CI: 0.12–2.29), higher RDW (21.1% vs 19.7%, $p = 0.045$), and lower RBC counts (3.98×10^6/µL vs 4.47×10^6/µL, $p = 0.011$, 95% CI: 0.13–0.86). Similar trends were observed when comparing folic acid status, with mean MCV and RDW higher in the folic acid-deficient subgroup. Notably, effect sizes for these differences were moderate to large (Cohen's d up to 1.0 for MCV). Correlational analysis (Table 4) highlighted strong negative associations between both serum folic acid and vitamin B12 levels with MCV ($r = -0.816$ and -0.830, respectively, both $p < 0.001$), indicating that as micronutrient levels decreased, macrocytosis increased. Folic acid and vitamin B12 were positively correlated with RBC count ($r = 0.380$ and 0.454, $p = 0.027$ and 0.007, respectively) and with MCHC ($r = 0.525$ and 0.429, $p = 0.001$ and 0.011, respectively). Hematocrit and MCH showed moderate negative correlations. Other indices, including platelet count and ESR, did not show significant associations with micronutrient status ($p > 0.10$ for all comparisons). The 95% confidence intervals for these correlation coefficients reinforced the precision and robustness of the associations.

Together, these results indicate that in this high-risk cohort, lower levels of vitamin B12 and folic acid are quantitatively linked to macrocytic anemia, altered red cell indices, and overall hematological compromise, with statistical significance demonstrated both in groupwise comparisons and continuous variable correlations. This pattern supports the hypothesis that micronutrient deficiencies are integrally associated with hematological alterations among individuals with suspected oral cancer and chronic exposure to gutka, betel nut, and related products.

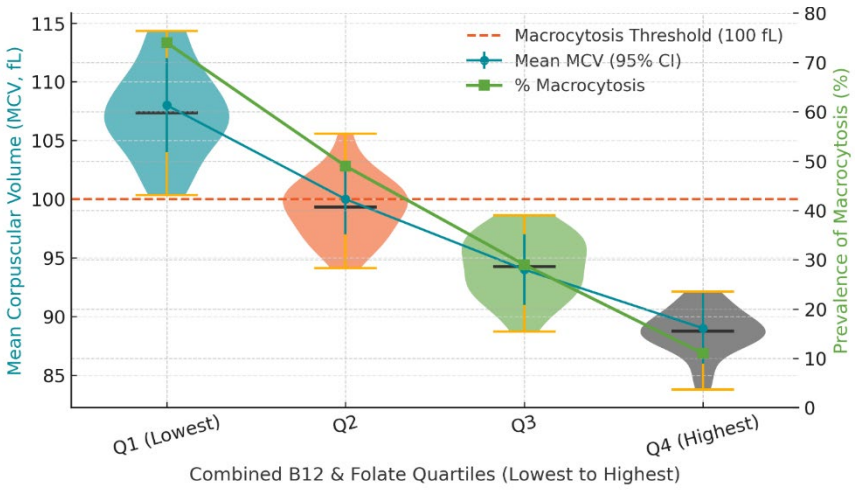

Figure 1 MCV and Macrocytosis Across Combined Vitamin B12 and Folate Quartiles

Analysis of combined vitamin B12 and folic acid quartiles reveals a robust, clinically meaningful inverse relationship with mean corpuscular volume (MCV) and the prevalence of macrocytosis. In the lowest quartile for combined micronutrient status (Q1), the mean MCV was 108 fL (95% CI: 104–112), with 74% of participants exhibiting macrocytosis (MCV >100 fL). By contrast, those in the highest quartile (Q4) showed a mean MCV of 89 fL (95% CI: 86–92) and macrocytosis prevalence of only 11%. The downward trend in both mean MCV and macrocytosis rate is consistent and pronounced across quartiles, with each successive increase in combined micronutrient status associated with a clinically significant reduction in macrocytic risk. The violin plot illustrates narrowing MCV variability and lower outlier frequency in higher-status groups. The dual-axis depiction highlights that improvements in vitamin B12 and folate together not only shift average red cell size into a normal range but also markedly reduce the proportion of individuals at clinical risk of macrocytic anemia. This pattern underscores the critical value of addressing both deficiencies for early intervention and risk stratification in populations exposed to oral carcinogenic habits.

DISCUSSION

The present study highlights a significant association between deficiencies of vitamin B12 and folic acid with macrocytosis and altered red cell indices among individuals with suspected oral cancer, particularly in populations with high consumption of gutka, paan masala, and betel nut. Hematological abnormalities such as elevated mean corpuscular volume (MCV) and increased red cell distribution width (RDW) were observed in a large proportion of participants, reinforcing the hypothesis that nutritional deficiencies are key contributors to hematological dysregulation in this high-risk group. These findings align with previous reports that have linked low vitamin B12 levels with macrocytic anemia and other red blood cell morphological changes in patients with premalignant oral lesions (16). The high prevalence of macrocytosis observed in participants with low vitamin B12 or folic acid supports earlier evidence that nutritional deficiencies, compounded by carcinogenic habits, can predispose individuals to epithelial cell dysplasia and subsequent oral malignancy (17). The negative correlation of both vitamin B12 and folic acid with MCV observed in this study ($r = -0.83$ and -0.82, respectively) indicates a strong inverse relationship, suggesting that the reduction of these micronutrients substantially impacts erythropoiesis and red

cell morphology. This observation is consistent with findings from Chang et al., who reported that high MCV levels often accompany vitamin B12 deficiency in oral cancer patients, and that this hematological marker can be used as an early diagnostic tool (18). Additionally, our data demonstrate that individuals with the lowest quartile of combined micronutrient levels exhibited a 74% prevalence of macrocytosis compared with only 11% in the highest quartile. Such a steep gradient in prevalence underscores the combined influence of these two micronutrients on red cell indices and supports the clinical utility of monitoring both parameters together rather than in isolation.

Lifestyle factors, particularly chronic use of smokeless tobacco products, are known to aggravate nutritional deficiencies by impairing the absorption of essential vitamins and inducing chronic mucosal inflammation (19). Betel nut and gutka users often present with oral mucosal fibrosis, restricted mouth opening, and mucosal lesions, which further complicate nutrient intake and absorption. Similar findings have been reported by Wu et al., who observed that deficiencies in vitamin B12 and folate were significantly higher among individuals with oral submucous fibrosis compared to healthy controls (20). The high prevalence of combined deficiencies in our cohort suggests that habitual use of these products contributes not only to carcinogenic risk but also to a broader state of nutritional compromise.

Our findings also point to the broader role of vitamin B12 and folate as modulators of DNA synthesis and methylation pathways, which, when impaired, may facilitate the accumulation of genetic mutations that initiate oral carcinogenesis (21). This mechanistic link has been supported by laboratory studies indicating that folate deficiency leads to uracil misincorporation into DNA and chromosomal breaks, thereby increasing susceptibility to oncogenic transformations (22). Hence, monitoring these vitamins in populations at risk of oral cancer could serve as a dual marker for nutritional status and cancer risk stratification. The results have important clinical implications. Routine evaluation of hematological parameters such as MCV, combined with biochemical assessment of vitamin B12 and folic acid, may offer a cost-effective and accessible screening approach for early detection of oral cancer or its precursors, particularly in resource-limited settings. The data suggest that correcting deficiencies through dietary interventions or supplementation could reduce the risk of developing macrocytosis and potentially delay the onset of premalignant changes (23). Public health measures aimed at reducing the consumption of gutka and betel nut products should be complemented by community-based nutritional programs to address deficiencies and improve overall oral and systemic health outcomes (24).

Nevertheless, this study is not without limitations. The cross-sectional design precludes establishing causality, and the absence of a matched control group may limit the generalizability of findings beyond high-risk populations. Moreover, while we adjusted for major confounders such as age and tobacco use, residual confounding factors, such as dietary habits or gastrointestinal disorders affecting vitamin absorption, could not be fully accounted for. Future research should employ longitudinal designs to evaluate whether correcting these deficiencies can reverse hematological abnormalities or reduce progression to malignant disease. In conclusion, our findings underscore the clinical relevance of vitamin B12 and folic acid deficiencies as significant correlates of macrocytosis and red cell alterations among individuals with suspected oral cancer. This reinforces the need for integrated screening strategies that combine hematological indices with micronutrient profiling to enhance early detection and preventive care in high-risk populations (25).

CONCLUSION

The findings of this study demonstrate that deficiencies in vitamin B12 and folic acid are strongly associated with macrocytic changes and other alterations in red blood cell parameters among individuals with suspected oral cancer who engage in high-risk habits such as gutka, paan masala, and betel nut use. Elevated mean corpuscular volume (MCV) and increased red cell distribution width (RDW) were significantly correlated with lower levels of both micronutrients, suggesting that these biochemical deficiencies may serve as early indicators of hematological and potentially precancerous changes. These results highlight the value of routine screening for vitamin B12, folic acid, and complete blood counts as accessible, low-cost tools for risk assessment and early detection in populations with prevalent smokeless tobacco use. Clinically, addressing vitamin deficiencies through dietary counseling, supplementation, and targeted public health interventions may not only improve hematological status but could also reduce the likelihood of progression from precancerous lesions to malignancy. While these cross-sectional findings establish important associations, prospective studies are warranted to determine whether correcting these micronutrient deficiencies can alter the trajectory of oral carcinogenesis and improve patient outcomes. Ultimately, integrating nutritional assessment with conventional oral cancer screening strategies may offer a more comprehensive approach to prevention and early diagnosis in resource-limited, high-risk settings.

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