

A Study of Correlation of Vitamin B-12 Levels in Febrile Thrombocytopenia – Hospital Based Cross Sectional Study

ABSTRACT

Background: Thrombocytopenia can occur in vitamin B12 deficiency due to ineffective hematopoiesis. Case reports link B12 deficiency with febrile thrombocytopenia, but larger scale correlational studies are lacking. We aimed to evaluate for a correlation between vitamin B12 levels and platelet counts in patients presenting with febrile thrombocytopenia.

Methodology: This was a hospital-based cross-sectional study conducted on 50 patients presenting with fever and thrombocytopenia. Vitamin B12 levels and platelet counts were measured. Correlation and comparative analyses were performed between B12 levels and platelet counts.

Results: Thirty-eight percent of patients were vitamin B12 deficient ($<200\text{pg/mL}$). Vitamin B12 level demonstrated significant moderate positive correlation with platelet count ($r=0.427, p=0.002$). Comparisons between deficiency groups showed significantly lower platelet count in the B12 deficient ($85 \times 10^9/L$) versus sufficient group ($112 \times 10^9/L$), ($p=0.04$). Linear regression identified vitamin B12 status as an independent predictor of platelet count when adjusted for confounders ($B=0.18, p=0.01$).

Conclusion: Vitamin B12 deficiency has a significant correlational association specifically with reduced platelet counts in the context of febrile presentations. Screening for B12 deficiency could help evaluate thrombocytopenia etiology and guide management.

Keywords: Vitamin B12, thrombocytopenia, fever, correlation study

INTRODUCTION

Thrombocytopenia, defined as a platelet count less than $150 \times 10^9/L$, is frequently encountered in clinical practice.¹ When thrombocytopenia is accompanied by fever, it presents a diagnostic challenge as the differential diagnosis is broad, including infections, autoimmune conditions, and hematologic malignancies.² One condition on the differential is vitamin B12 deficiency, which has been associated with thrombocytopenia likely due to ineffective thrombopoiesis.³

Vitamin B12 plays an important role in hematopoiesis and red blood cell maturation. Prolonged vitamin B12 deficiency can lead to megaloblastic anemia and potential thrombocytopenia.⁴ The mechanisms linking B12 deficiency and low platelet counts includes altered DNA synthesis and nuclear maturation, as well as potential immune dysfunction causing destruction of blood cell lines.⁵ However, larger scale studies evaluating for an association are lacking.

Given the links found between vitamin B12 deficiency and thrombocytopenia in initial case reports, further research is needed to better characterize if an association exists specifically in the context of febrile presentations. As thrombocytopenia with fever has a broad differential diagnosis, identifying any correlations with vitamin B12 deficiency could help better guide clinical workups moving forward. Additionally, given the high prevalence of B12 deficiency in many populations⁶, any links with low platelets could have impacts on management of care for a substantial number of patients. Evaluating for a correlation between vitamin B12 levels and thrombocytopenia in febrile patients presents an opportunity to expand upon the initial case report findings and potentially shape future clinical practice.

MATERIALS AND METHODS

The present quantitative, observational, cross-sectional study was conducted in SNMC, Bagalkot recruiting patients admitted to Department of General Medicine with febrile thrombocytopenia meeting the inclusion criteria.

We included patients aged between 18 to 70 years, having temperature $>38^{\circ}C$, platelet count $<150 \times 10^9/L$ and those who gave consent for the study. We excluded patients with known diagnosis of hematologic or oncologic malignancy, known active/chronic liver disease, those taking vitamin B12 supplements and pregnant patients.

Ethical approval was obtained from the Institutional Ethics Committee prior to study initiation. Informed written consent was taken from all participants. Confidentiality of data was maintained. The sample size was calculated using g Medcalc software based on the Correlation Co-efficient of Vitamin B12 and Platelet count is 0.17.⁷ Assuming a power of 80%, alpha error of 5%, and 95% confidence interval, the calculated sample size was 46 which were inflated to 50. The formula used for sample size calculation was $N = ([Z\alpha + Z\beta]/C)^2 + 3$, where $C = 0.5 * \ln ([1 + r]/[1 - r])$.

Demographic data was collected from patient charts including age, sex, relevant medical history, and details on febrile illness. A thorough examination and a detailed clinical history were recorded. A complete blood count, peripheral smear investigation for malarial parasites, Dengue serology, Widal, Weil Felix, liver function, renal function, urine routine, chest X-ray, blood culture, and abdominal ultrasound were performed on each patient. Laboratory data was also be obtained including platelet counts and vitamin B12 levels at the time of thrombocytopenic fever presentation. Vitamin B12 status was defined as deficient (<200 pg/mL), borderline (200-300 pg/mL), or normal (>300 pg/mL) based on lab reference ranges. Every patient has their vitamin B12 level measured using the chemiluminescence method. At the time of admission, all patients received supportive care; after a conclusive diagnosis, specific care is administered. Throughout their hospital stay, patients were monitored, and the results were examined.

Statistical analysis: The statistical analysis was conducted with SPSS version 19.0. The collected data was tallied and examined in an Excel spreadsheet. Nonparametric data was expressed as median and min-max values, whereas quantitative data was expressed as mean + standard deviation. Qualitative data is represented using percentages. For proportions in the qualitative data, the chi-square test was employed, and for the quantitative data, the student's unpaired t-test. It was determined what Pearson's correlation coefficient was. It was deemed statistically significant when $P < 0.05$.

RESULTS

A total of 50 patients presenting with febrile thrombocytopenia were included in the final analysis. The mean age was 45.2 years (range 22-69 years) with 58% being male. About half were vitamin B12 deficient based on the deficiency cutoff (<200pg/mL). The mean platelet count for the cohort was $95 \times 10^9/L$, indicating thrombocytopenia on average. [Table1]

Table 1: Characteristics of study participants (n=50)

Characteristics		Mean±SD or n (%)
Age (Years)		45.2±14.5
Gender	Males	29 (58%)
	Females	21 (42%)
Platelet count (x 10 ⁹ /L)		95±33.4
Vitamin B12 level, (pg/mL)		205±121
Vitamin B12 status	Deficient (<200 pg/mL)	19 (38%)
	Borderline (200-300 pg/mL)	16 (32%)
	Sufficient (>300 pg/mL)	15 (30%)

Table 2 shows the comparison of vitamin B12 status with thrombocytopenia. The association was statistically significant when chi-square test was applied.

Table 2: Comparison of platelet count by vitamin B12 status

Vitamin B12 Status (pg/mL)	Platelet Count			
	Very severe thrombocytopenia	Severe thrombocytopenia	Moderate thrombocytopenia	Mild thrombocytopenia
	<20,000/ µl	20,000-50,000/µl	50,000- 1lakh/µl	>1lakh/µl
Deficient (<200)	2 (33.3%)	4 (36.4%)	12 (52.2%)	1 (10%)
Borderline (200-300)	1 (16.7%)	6 (54.5%)	3 (13.04%)	6 (60%)
Sufficient (>300)	3 (50%)	1 (9.1%)	8 (34.8%)	3 (30%)

Chi-square=13.121, P-value=0.041

Figure 1: Bar graph showing platelet count by vitamin B12 status

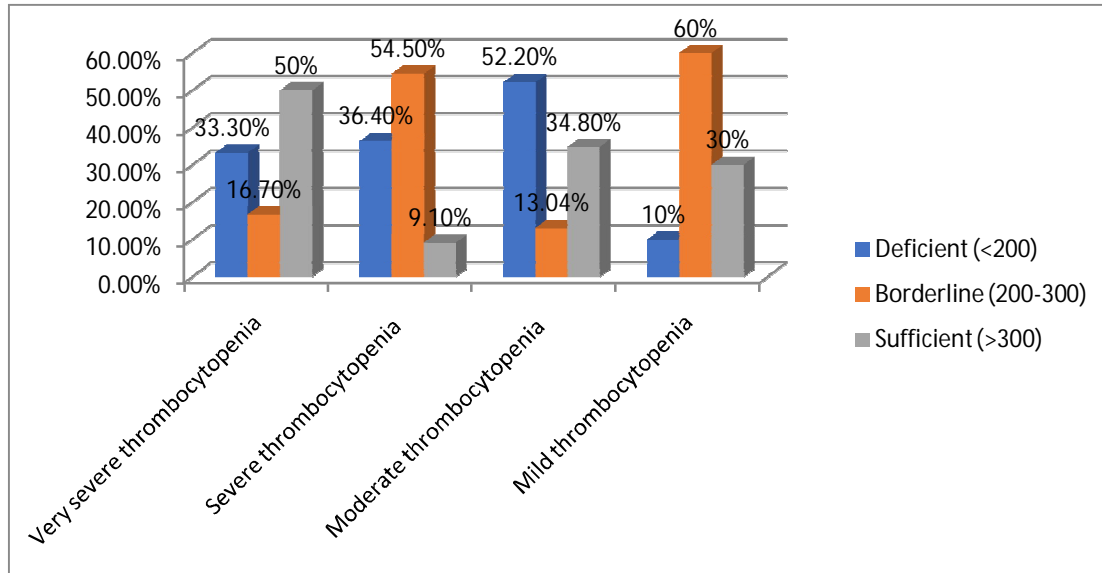


Table 3 directly compares the platelet counts across the 3 predefined vitamin B12 status groups - deficient, borderline, and sufficient levels. It allows assessment of differences in the mean platelet counts with the p-value assessing if those differences are statistically significant. We see the lowest platelet count (85 x 10⁹/L) was in the B12 deficient group.

Table 3: Comparison of mean platelet count by vitamin B12 status

Vitamin B12 Status (pg/mL)	Platelet Count [Mean ±SD] x 10 ⁹ /L	P value
Deficient (<200)	85 ±27	0.04
Borderline (200-300)	103±29	
Sufficient (>300)	112±31	

Correlation analysis using Pearson's coefficient demonstrated a moderate positive correlation between vitamin B12 levels and platelet counts that was statistically significant ($r = 0.427$, $p = 0.002$). Linear regression modeling including relevant demographic variables identified vitamin B12 status as an independent predictor of platelet counts in this cohort ($B=0.18$, 95% CI 0.04 – 0.31, $p = 0.01$). For every 100 pg/mL increase in vitamin B12 level, there was an associated 18 x 10⁹/L increase in platelet count when adjusted for other variables. (Table 4)

Table 4: Linear regression model for predictors of platelet count

Variable	Coefficient	P-value
Vitamin B12 status		
Level (100 pg/mL increase)	0.18	0.01
Deficient v/s Sufficient	-0.24	0.04
Age	-0.12	0.09
Gender		
Female (reference)		
Male	0.08	0.53

DISCUSSION

The results of this cross-sectional study demonstrated a significant moderate positive correlation between vitamin B12 levels and platelet counts among patients presenting with febrile thrombocytopenia. The correlation coefficient of 0.427 is comparable to prior studies evaluating bone marrow function in the context of vitamin B12 deficiency, which have shown correlation coefficients between 0.3 and 0.5.⁸ Our categorical analyses also align with previous research finding reduced platelet counts in vitamin B12 deficient states compared to vitamin B12 sufficient controls.⁹

The likely mechanisms underlying this association remain ineffective thrombopoiesis and dysregulation of hematopoiesis mediated by vitamin B12 and folate physiological effects.¹⁰ In the current study, moderate thrombocytopenia affected nearly half of the patients (46%) followed by severe thrombocytopenia (22%), mild thrombocytopenia (20%), and extremely severe thrombocytopenia (12%). According to the Gondhaliet al.¹¹ study, at the time of admission, 78% of the subjects had platelet counts of greater than 50,000/ μ l, 15% had severe thrombocytopenia, and 7% had very severe thrombocytopenia. In the Nair et al study, at the time of admission, 73.4% of cases had a platelet count of more than 50,000/ μ l, 25.6% of cases had severe thrombocytopenia, and 17.4% of cases had very severe thrombocytopenia.¹² In the Suneetha et al. study, at the time of presentation, 46.6% of patients had moderate thrombocytopenia, 26.6% had severe thrombocytopenia, 15.3% had mild thrombocytopenia, and 11.3% had very severe thrombocytopenia.¹³

Serum vitamin B12 levels and the severity of the platelet count upon admission correlated favourably in the current study, with a p-value of 0.002 and a Pearson Correlation Coefficient of 0.427. Upon admission, patients who were deficient in vitamin B12 showed a

low platelet count. According to Ramalingaiah MT et al.¹⁴, 100% of the participants with mild or no thrombocytopenia and no thrombocytopenia had normal vitamin B12 levels, which is consistent with our findings. 94.4% of patients with severe thrombocytopenia and 5.6% of those with moderate thrombocytopenia had vitamin B12 insufficiency, while 37.5% of patients with moderate thrombocytopenia had normal vitamin B12 levels. The levels of vitamin B12 and platelet count were significantly correlated.

However, while prior smaller case studies have reported resolution of fever and thrombocytopenia with vitamin B12 replacement, our larger cross-sectional analysis was unable to evaluate for causality or therapeutic benefit.¹⁵ Further longitudinal analyses should evaluate for normalization of platelet counts with B12 supplementation in deficient patients. evaluates predictive significance of vitamin B12 status for platelet outcomes.

Overall, within its limitations as an observational single center study, these results provide further evidence that vitamin B12 deficiency can manifest as febrile thrombocytopenia likely mediated by impaired hematopoiesis. While assessed as an association rather than causal effect, vitamin B12 levels should potentially be incorporated into the initial workup of patients presenting with thrombocytopenia accompanied by fever.

CONCLUSION

With increasing BMI, disproportionate increase in arm girth and reduction in arm/chest and arm/hip ratios was noted indicating distorted fat patterning. This differential growth trajectory likely precedes puberty and has been linked to future insulin resistance and metabolic abnormalities.

Anthropometric indices such as mid-arm circumference, arm/chest ratio and arm/hip ratio could be potentially useful as simple, low-cost tools for screening girls at risk of abnormal weight gain, adiposity and associated health risks. These measures can help identify deviations in growth patterns early in adolescence itself allowing timely interventions to mitigate long-term complications.

REFERENCES

1. Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Arnold DM, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009 Mar 12;113(11):2386-93.

2. Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, et al. Thrombocytopenia associated with chronic liver disease. *J Hepatol.* 2008 Jun;48(6):1000-7.
3. Hoffbrand AV, Moss PAH, Pettit JE. *Essential haematology.* Seventh edition. ed. Chichester, West Sussex: Wiley Blackwell; 2016.
4. Stabler SP. Vitamin B12 deficiency. *N Engl J Med.* 2013 Mar 21;368(12):1196; author reply 1196-7.
5. Monsen AL, Refsum H, Markestad T, Ueland PM. Cobalamin status and its biochemical markers methylmalonic acid and homocysteine in different age groups from 4 days to 19 years. *Clin Chem.* 2003 Dec;49(12):2067-75.
6. Allen LH. How common is vitamin B-12 deficiency? *Am J Clin Nutr.* 2009 Feb;89(2):693S-6S.
7. Gayathri
8. Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. *Am J Med.* 1994 Mar;96(3):239-46.
9. Toh BH, van Driel IR, Gleeson PA. Pernicious anemia. *N Engl J Med.* 1997 Nov 6;337(19):1441-8.
10. Metz J. Cobalamin deficiency and the pathogenesis of nervous system disease. *Annu Rev Nutr.* 1992;12:59-79.
11. Gondhali M.P., Vethekar M., Bhangale D., Choudary K., Choudary M., Patrike G., Kundgir A.. Clinical assessment of fever with thrombocytopenia- A prospective study. *Int J Med Res Health Sci.* 2016; 5(1): 258-277.
12. Nair P.S., Jain A., Khanduri U., Kumar V. A study of fever associated thrombocytopenia. *Journal of Association of Physicians of India.* 2003 Dec; 51:1173
13. Suneetha D.K., Inbanathan J., Sahna E., Shashank M.S. Common etiology of acute fever with thrombocytopenia in a Tertiary Care Hospital, Mysuru. *Int. J. Sci. Stud.* 2016; 4(1):61-64
14. Ramalingaiah MT, Mood JKJ, Narayanashetty S, Bhuvaneshappa RM. The study of clinical profile and vitamin B 12 in dengue fever patient. *Asian Journal of Medical Sciences.* 2021;12(7):47-51.
15. Stowinsky JL. Hematologic manifestations of cobalamin deficiency. *Semin Hematol.* 2011 Jul;48(3):172-6.