Indigenous indicators of vitamin B12 deficiency

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ABSTRACT

Introduction: Clinical manifestations of vitamin B12 deficiency are mostly non-specific. An entity called subclinical deficiency has become popular where the need has arisen to perform costly investigations which indicate functional deficiency of vitamin B12 even when vitamin B12 levels are normal. These factors pose a challenge in planning management of patients.

Aims and objectives : The study was conducted as an attempt to identify affordable and credible laboratory indicators of vitamin B12 deficiency which can be used as screening tests before choosing patients for further evaluation or treatment.

Material and Methods : This was a time bound cross-sectional study where 100 adult patients who had undergone the following investigations were randomly chosen: Complete Blood Count with red cell indices, serum bilirubin and serum vitamin B12 levels. The sensitivity, specificity and predictive values (positive-PPV and negative-NPV) of the variables that could hypothetically identify vitamin B12 deficiency, both individually or in combinations were calculated and compared.

Results and conclusion : Hemoglobin, MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), platelets and bilirubin were not equally distributed between vitamin B12 deficient and normal groups(p values for these variables were 0.029, 0.000, 0.000, 0.003 and 0.029 respectively).When these variables were tested individually and in combination, the combination of [MCV=95 fl or MCH=30 pg or Platelets =1.4 lakh/µl or Bilirubin =1 mg/dl] had sensitivity of 68.2%, specificity of 85.7%, PPV of 78.9% and NPV of 77.4%. This proposed combination used as a screening test has potential for wide application considering its simplicity and cost advantage.

Key words: Cobalamin deficiency, Erythrocyte Indexes, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Red Cell Indices

Article :

Introduction

Clinical manifestations of vitamin B12 deficiency are diverse and mostly non-specific. An entity called subclinical deficiency has become popular where patients with possible clinical manifestationsof vitamin B12 deficiency and vitamin B12 levels in the lower range but not deficient are being empirically treated with vitamin B12 injections and tablets. As the patients with vitamin B12 levels in the normal range are also being considered for treatment, the need has arisen to test for elevation in other biomarkers like methylmalonic acid (MMA) and/or homocysteine which may indicate functional deficiency of vitamin B12. Further, the reported normal vitamin B12 levels in labs are of wide range and false high vitamin B12 levels are reported in inflammatory diseases.[1]

These factors pose a challenge for physicians in selecting patients for further investigations and treatment of vitamin B12 deficiency.Especially in a country like India where we are still pursuing the dream of affordable treatment to all, it will be valuable if we have low cost indicators that will assist us in selecting patients for further evaluation or treatment of vitamin B12 deficiency.

Material and Methods

This was a time bound cross sectional study conducted in B.J.Medical College, Ahmedabad and attached tertiary care hospital over a period of two years where100 adult patients who had undergone the following investigations were randomly chosen.

- Complete Blood Count with red cell indices
- Serum Bilirubin
- Serum vitamin B12 levels

Hematology analyzer used: Automated hematology cell counter –cell-dyn 3700sl

Serum vitamin B12 assay was done by Chemiluminescence immune assay method using Abbott ARCHITECT.

Operational definition:

Participants were classified as vitamin B12 deficient if serum vitamin B12 levels were ≤187 pg/ml and normal if vitamin B12 levels were ≥ 188pg/ml.

Statistical methods:

The data were analyzed using IBM SPSS Statistics v23. Continuous variables were expressed as mean ±standard deviation (SD). Test of normality (Shapiro-Wilk test) was used to determine whether the continuous variables were normally

distributed. Non-parametric tests like 2 groups Mann-Whitney U test and 2 sample Kolmogorov-Smirnov test were used for comparing homogenous and non-homogenous groups respectively. P value of <0.05 was considered significant.

The variables that could identify vitamin B12 deficiency were hypothetically tried as indicators of vitamin B12 deficiency, either individually or in combinations, and inferences were drawn.

Results :

The mean hemoglobin (Hb) of the study population was 11.64 g/dl (SD±2.76). The mean white blood cell (WBC) count of the study population was 8320.70 cells /µl (SD±3200.77). The mean of mean corpuscular volume (MCV) of the study population was 87.08 fl (SD±12.21). The mean of mean corpuscular hemoglobin (MCH) was 27.99 pg (SD±4.68). The mean red cell distribution width (RDW) was 15.21% (SD±3.11). The mean platelet count (PLT) was 2.43 lakh/µl (SD±0.92). Mean bilirubin was 0.51 mg/dl (SD±0.33). Mean vitamin B12 was 331.97 pg/ml (SD±270.31)

44 patients had serum B12 level of ≤187 pg/ml and were classified as vitamin B12 deficient and rest (56 participants) were classified as normal (non-deficient).

Hemoglobin, MCV, MCH, platelets and bilirubin were not equally distributed between vitamin B12 deficient and normal groups. p values for these variables were 0.029, 0.000, 0.000, 0.003 and 0.029 respectively. The distribution of WBC and RDW were same in both deficient and normal vitamin B12 level groups with p values of 0.255 and 0.839 respectively.

MCV, MCH, platelets and bilirubin were considered as possible indicators. The sensitivity, specificity, PPV (Positive Predictive Value) and NPV (Negative Predictive Value) of these parameters individually and in different combinations in identifying vitamin B12 deficiency were calculated and compared.

As observed in the table 4a, considering combination of either PLT ≤1.4lakh/µl or Bilirubin ≥1mg/dl as the initial screening test had the highest PPV of 90.9% with a specificity of 98.2% but had poor sensitivity of 22.7%. When these were considered along with MCV (≥90 or ≥95 fl) and MCH (≥30 or ≥31pg), the sensitivity of the screening combinations increased considerably with least being 65.9% and highest being 72.7%. Amongst these, the combination of **[MCV≥95flor MCH≥30pg or PLT≤1.4lakh/µl or Bilirubin≥1mg/dl]** had sensitivity of 68.2%, specificity of 85.7%, PPV of 78.9% and NPV of 77.4%. When serum bilirubin was not considered, the combination of other parameters as combined screening test **[MCV≥95fl or MCH≥30pg or PLT≤1.4lakh/µl]** had sensitivity of 65.9%, specificity of 87.5%, PPV of 80.6% and NPV of 76.6%.

Table 1: Distribution of variables in study population

Variables	Mean	Standard deviation
Hemoglobin (g/dl)	11.64	2.76
WBC (cells/µl)	8320.70	3200.77
MCV (fl)	87.08	12.21
MCH (pg)	27.99	4.68
RDW (%)	15.21	3.11
Platelets (lakh/µl)	2.43	0.92
Bilirubin (mg/dl)	0.51	0.33
Serum B12 (pg/ml)	331.97	270.31

Table 2: Distribution of variables in vitamin B12 deficient and non-deficient population

Variables	Deficient (n=44)		Non-deficient (n=56)	
	Mean	SD	Mean	SD
Hemoglobin (g/dl)	12.277	2.5047	11.142	2.8738
WBC (cells/µl)	7788.64	3101.854	8738.75	3242.566
MCV (fl)	94.09	10.016	81.57	10.939

MCH (pg)	30.45	3.599	26.05	4.546
RDW (%)	15.27	2.944	15.16	3.252
Platelets (lakh/µl)	2.075	0.6634	2.711	0.9941
Bilirubin (mg/dl)	0.603	0.3779	0.441	0.2709
Serum B12 (pg/ml)	129.75	37.317	490.86	268.352

Table 3a: Sensitivity, specificity, PPV and NPV of MCV and MCH when considered individually as screening tests for vitamin B12 deficiency

Variables	Values	Sensitivity	Specificity	PPV	NPV
MCV (fl)	≥80	93.2	35.7	53.2	87
	≥85	77.3	58.9	59.6	76.7
	≥90	**68.2**	**78.6**	**71.4**	**75.9**
	≥95	**52.3**	**89.3**	**79.3**	**70.4**
	≥100	31.8	96.4	87.5	64.3
	≥105	18.2	98.2	88.9	60.4
	≥27	84.1	37.5	51.4	75
	≥28	79.5	50	55.6	75.7
	≥29	68.2	75	68.2	75
MCH (pg)	**≥30**	**63.6**	**87.5**	**80**	**75.4**
	≥31	**54.5**	**91.1**	**82.8**	**71.8**
	≥32	36.4	96.4	88.9	65.9
	≥33	29.5	96.4	86.7	63.5

Note: The parameters that were combined as a part of screening tests have been highlighted.

Table 3b: Sensitivity, specificity, PPV and NPV of platelet count (PLT) when considered individually as screening test for vitamin B12 deficiency

Variables	Values	Sensitivity	Specificity	PPV	NPV
PLT	≤4.4	100	7.1	45.8	100
	≤3.9	100	10.7	46.8	100
	≤3.4	97.7	25	50.6	93.3
	≤2.9	90.9	32.1	51.3	81.8
	≤2.4	72.7	50	53.3	70
(lakh/µl)	≤1.9	45.5	73.2	57.1	63.1
	≤1.4	13.6	100	100	59.6

	≤0.9	6.8	100	100	57.7
	≤0.4	2.3	100	100	56.6

Note: The parameter that was combined as a part of screening tests has been highlighted.

Table 3c: Sensitivity, specificity, PPV and NPV of serum bilirubin when considered individually as screening test for vitamin B12 deficiency

Variables	Values	Sensitivity	Specificity	PPV	NPV
Bilirubin (mg/dl)	≥0.2	95.3	3.6	43.2	50
	≥0.3	81.4	26.8	46.1	65.2
	≥0.4	70.5	48.2	51.7	67.5
	≥0.5	61.4	62.5	56.3	67.3
	≥0.6	56.8	71.4	61	67.8
	≥0.7	40.9	76.8	58.1	62.3
	≥0.8	22.7	89.3	62.5	59.5
	≥0.9	15.9	92.9	63.6	58.4
	≥1.0	11.4	98.2	83.3	58.5
	≥1.1	11.4	98.2	83.3	58.5
	≥1.2	9.1	98.2	80	57.9
	≥1.3	6.8	98.2	75	57.3

Note: Note: The parameter that was combined as a part of screening tests has been highlighted.

Table 4a: Two parameters as combined screening tests for vitamin B12 deficiency

Parameters	Combinations	Sensitivity	Specificity	PPV	NPV
MCV or MCH	MCV≥90 or MCH≥30	68.2	78.6	71.4	75.9
	MCV≥90 or MCH≥31	68.2	78.6	71.4	75.9
	MCV≥95 or MCH≥30	63.6	87.5	80	75.4
	MCV≥95 or MCH≥31	61.4	89.3	81.8	74.6
MCH or PLT	MCV≥90 or PLT≥1.4	70.5	78.6	72.1	77.2
	MCV≥95 or PLT≥1.4	54.5	89.3	80	71.4
MCV or Bilirubin	MCH≥30 or PLT≥1.4	65.9	87.5	80.6	76.6
	MCH≥31 or PLT≥1.4	56.8	91.1	83.3	72.9
MCH or Bilirubin	MCV≥90 or Bilirubin≥1	70.5	76.8	70.5	76.8
	MCV≥95 or Bilirubin≥1	54.5	87.5	77.4	71

MCH or Bilirubin	MCH≥30 or Bilirubin≥1	65.9	85.7	78.4	76.2
	MCH≥31 or Bilirubin≥1	61.4	89.3	81.8	74.6
PLT or Bilirubin	PLT≤1.4 or Bilirubin≤1	22.7	98.2	90.9	61.8

Table 4b: Three red cell indices as combined screening tests for vitamin B12 deficiency

Parameters	Combinations	Sensitivity	Specificity	PPV	NPV
MCV or MCH or PLT	MCV≥90 or MCH≥30 or PLT≤1.4	70.5	78.6	72.1	77.2
	MCV≥95 or MCH≥30 or PLT≤1.4	65.9	87.5	80.6	76.6
	MCV≥90 or MCH≥31 or PLT≤1.4	70.5	78.6	72.1	77.2
	MCV≥95 or MCH≥31 or PLT≥1.4	63.6	89.3	82.4	75.8

Table 4c: Three parameters (including red cell indices and bilirubin) as combined screening tests for vitamin B12 deficiency

Parameters	Combinations	Sensitivity	Specificity	PPV	NPV
MCV or MCH or PLT	MCV≥90 or PLT≤1.4 or Bilirubin≥1	72.7	76.8	71.1	78.2
	MCV≥95 or PLT≤1.4 or Bilirubin≥1	56.8	87.5	78.1	72.1
MCH or PLT or Bilirubin	MCH≥30 or PLT≤1.4 or Bilirubin≥1	68.2	83.9	78.9	77
	MCH≥31 or PLT≤1.4 or Bilirubin≥1	63.6	89.3	82.4	75.8
	MCV≥90 or MCH≥30 or Bilirubin≥1	70.5	76.8	70.5	76.8
MCV or MCH or Bilirubin	MCV≥95 or MCH≥30 or Bilirubin≥1	65.9	85.7	78.4	76.2
	MCV≥90 or MCH≥31 or Bilirubin≥1	70.5	76.8	70.5	76.8
	MCV≥95 or MCH≥31 or Bilirubin≥1	63.6	87.5	80	75.4

Table 4d: Four parameters as combined screening tests for vitamin B12 deficiency

Parameters	Combinations	Sensitivity	Specificity	PPV	NPV
MCV or MCH or PLT	MCV≥90 or MCH≥30 or PLT≤1.4 or Bilirubin≥1	72.7	76.8	71.1	78.2
	MCV≥95 or MCH≥30 or PLT≤1.4 or Bilirubin≥1	68.2	85.7	78.9	77.4

	MCV≥90 or MCH≥31 or PLT≤1.4 or Bilirubin≥1	72.7	76.8	71.1	78.2
	MCV≥95 or MCH≥31 or PLT≤1.4 or Bilirubin≥1	65.9	87.5	80.6	76.6

Figure 1: Design of the study

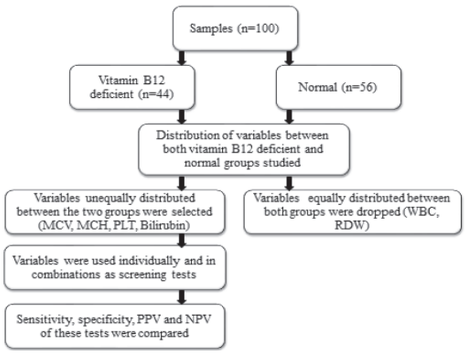


Figure 2: Vitamin B12 levels in study population

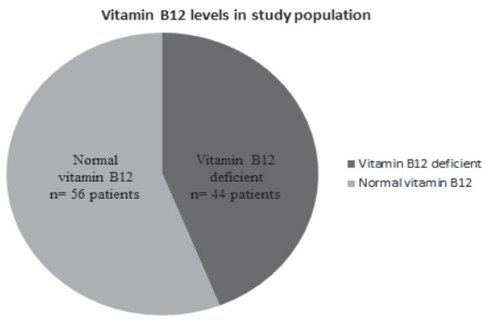


Figure 3: Distribution of hemoglobin in vitamin B12 deficient and normal groups

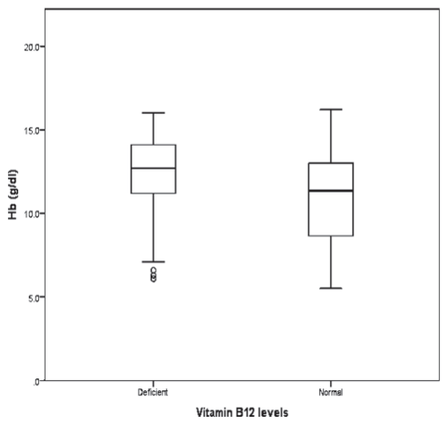


Figure 4: Distribution of MCV in vitamin B12 deficient and normal groups

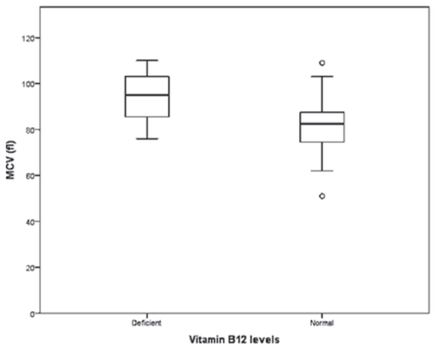


Figure 5: Distribution of MCH in vitamin B12 deficient and normal groups

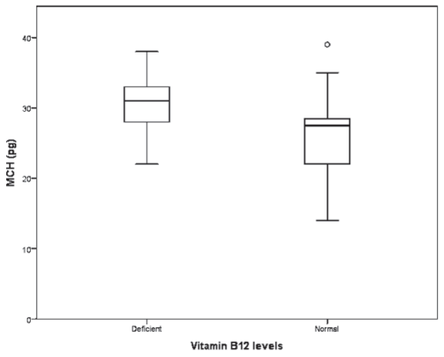


Figure 6: Distribution of platelets in vitamin B12 deficient and normal groups

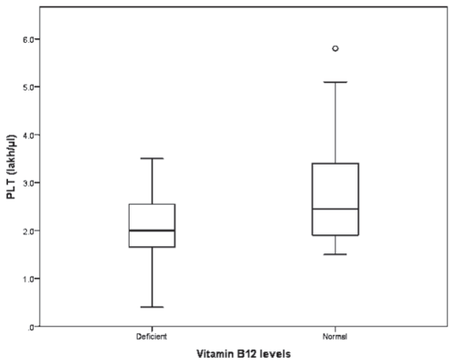
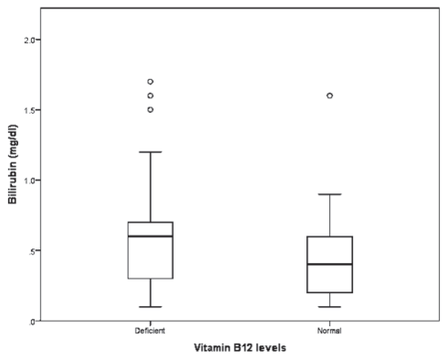


Figure 7: Distribution of bilirubin in vitamin B12 deficient and normal groups



Discussion

Neurological and hematological manifestations of vitamin B12 deficiency are very non-specific. Neurological manifestations can range from mild confusion to obvious neurological deficits as seen in sub-acute combined degeneration of spinal cord. Hematological manifestations are mainly due to anemia and hypoproliferation of other marrow elements which can also be seen in many other diseases.[1,2]

Once vitamin B12 deficiency is suspected an array of tests are available to confirm its presence. Testing serum vitamin B12 levels currently remains the first-line test, with plasma methylmalonic acid (MMA) or homocysteine being used as second-line tests to help clarify uncertainties of underlying biochemical/functional deficiencies. Serum holotranscobalamin has been said to have the potential to be a first-line test.[3,4]

Occasionally as deficiency develops, serum B12 values may be maintained at the expense of vitamin B 12 in the tissues. In such cases serum homocysteine and MMA levels are estimated to identify functional deficiency of vitamin B12.However, these have the major flaw of poor specificity. Vitamin B12 deficiency accounts for only a minority of all high homocysteine or MMA levels and can easily be confused with other common causes like renal failure. Also the reference interval is not universally agreed, and creatinine levels must always be taken into account when interpreting mild elevations of these biomarkers.High cost and low availability have also limited their use.The current scenario has created a major setback to rational management of vitamin B12 deficiency, especially with the added burden of subclinical deficiency.[3,4]

Vitamin B12 is necessary for the normal DNA (deoxyribonucleic acid) synthesis. Deficiency of this vitamin can result in megaloblastic changes producing oval macrocytes and other abnormally shaped erythrocytes that appear in the blood. This leads to increase in red cell distribution width as well as mean corpuscular volume. As the megaloblastic changes occur in all rapidly dividing cells in the marrow, neutropenia and thrombocytopenia can also be present in vitamin B12 deficiency, sometimes much before anemia. It is also suggested that ineffective erythropoiesis may cause immature erythrocyte formation increasing hemolysis and levels of indirect bilirubin in blood.[5]

Peripheral smear examination may reveal presence of macrocytosis, hypersegmented neutrophils, anisocytosis or poikilocytosis in a patient with vitamin B12 deficiency.

Information provided by the automated cell counter indicative of vitamin B12 deficiency includes decreased hemoglobin (Hb), raised mean corpuscular volume (MCV), normal or decreased mean corpuscular hemoglobin concentration (MCHC), broadening of red cell distribution width (RDW) and low reticulocyte index.The tendency of MCH to increase or decrease follows MCV. Vitamin B12 deficiency is usually associated with *normochromic or hypochromic cells* resulting in MCHC within or below the reference range. As hemoglobin makes up approximately 33% of the volume of the cell, erythrocytes cannot carry more hemoglobin in their cytoplasm than normal, so they cannot be hyperchromic. An increased MCHC is usually associated with hemolysis, either a result of disease or of improper venipuncture or sample handling.[6,7]

MCV defines the size of the red blood cells and is expressed as femtoliters (10^{-15}; fl) or as cubic microns (μm^3). The normal values for MCV are 87 ± 7 fl. MCH quantifies the amount of hemoglobin per red blood cell. The normal values for MCH are 29 ± 2 picograms (pg) per cell.

MCHC indicates the amount of hemoglobin per unit volume. In contrast to MCH, MCHC correlates the hemoglobin content with the volume of the cell. It is expressed as g/dl of red blood cells or as a percentage value. The normal values for MCHC are 34 ± 2 g/dl. RDW represents the coefficient of variation of the red blood cell volume distribution (size) and is expressed as a percentage. The normal value for RDW is 13 ± 1.5%.[8]

Termed *red cell indices,* these values have been useful in elucidating the etiology of anemias. A study which attempted to use MCV as a screening parameter for vitamin B12 deficiency had found that it was unreliable as an individual parameter.[9] Also, we found studies which tried to use parameters derived from the blood cell count obtained using simple counters to differentiate iron deficiency anemia from thalassemia trait.[10,11] Similar attempt was made in this study where the idea was extended to develop and validate an index using red cell indices and serum bilirubin that can be used as a screening parameter for vitamin B12 deficiency.

When the distribution of different variables in the study population was observed it was found that hemoglobin, MCV, MCH, platelets and bilirubin were not equally distributed

between vitamin B12 deficient and normal groups. *p* values for these variables were 0.029, 0.000, 0.000, 0.003 and 0.029 respectively. The distribution of WBC and RDWwere same in both deficient and normal vitamin B12 level groups with p values of 0.255 and 0.839 respectively.

It was also found that mean MCV, MCH and bilirubin were higher and platelet count was lower in participants with vitamin B12 deficiency when compared to participants with normal vitamin B12 levels, as expected. Though anemia is one of the common clinically observable manifestations of vitamin B12 deficiency mean hemoglobin level was more in vitamin B12 deficient group than in normal group. This suggested that anemia as an individual criterion is neither specific nor sensitive to vitamin B12 deficiency and was dropped from the list of possible indicators of vitamin B12 deficiency. Only MCV, MCH, platelets and bilirubin were then considered as possible indicators.

The sensitivity and specificity of these parameters individually and in different combinations in identifying vitamin B12 deficiency were calculated and compared as shown in table 3 (3a, 3b, 3c) and 4 (4a, 4b, 4c, 4d).Since performance of a screening test is measured by its 'predictive value' which depends on sensitivity, specificity and prevalence of the disease, the positive predictive value (PPV) and negative predictive value (NPV) were also calculated for each test and compared.[12]

While selecting parameters to use in various combinations it was made sure that they fulfilled the following two criteria so that sensitivity could be increased without sacrificing the specificity or PPV:

1) The selected value is an early indicator of vitamin B12 deficiency under considered parameter.

2) The value of a screening test had specificity of more than 75% and PPV of more than 70%.

The parameters which satisfied the above criteria have been highlighted in table 3(3a, 3b, 3c).

As observed in the table 4a, considering combination of either PLT≤1.4lakh/µl or Bilirubin≥1mg/dl as the initial screening test had the highest PPV of 90.9% with a specificity of 98.2% but had poor sensitivity of 22.7%.

However when these were considered along with MCV (≥90 or ≥95 fl) and MCH (≥30 or ≥31pg), the sensitivity of the screening combinations increased considerably with least being 65.9% and highest being 72.7%.

Amongst these the combination of **[MCV≥95 fl or MCH≥30 pg or PLT≤1.4 lakh/µl or Bilirubin≥1 mg/dl]**had sensitivity of 68.2%, specificity of 85.7%, PPV of 78.9% and NPV of 77.4%. Even when serum bilirubin was not considered the combination of other parameters as combined screening test**[MCV≥95 fl or MCH≥30 pg or PLT≤1.4 lakh/µl]** had sensitivity of 65.9%, specificity of 87.5%, PPV of 80.6% and NPV of 76.6%. Epidemiological studies show that in the general population of India, vitamin B12 deficiency has a prevalence of 47%.13 Also studies focusing on elderly people, particularly those who are in institutions or who are sick and malnourished, have estimated a prevalence of vitamin B12 deficiency as 30–40%.[14,15] In this study the prevalence of vitamin B12 deficiency was 44%. Therefore it could be inferred that the diagnostic power of the proposed screening test in communities of similar prevalence of vitamin B12 deficiency may remain the same.

These results showed that the sensitivity of the proposed combinations to identify clinical vitamin B12 deficiency were moderate when compared with that of other routinely prescribed tests like serum homocysteine or MMA which is actually more than 95%. However, as the specificity of these metabolite assays remains undetermined, there has been concern that the use of metabolite assays as a gold standard for diagnosis of vitamin B12 deficiency may lead to over diagnosis and over treatment. Also the high cost and low availability limit their use as screening tests.[3,16,17]

Despite the moderate sensitivity for detecting patients with vitamin B12 deficiency application of the proposed combination **[MCV≥95 fl or MCH≥30 pg or PLT≤1.4 lakh/µl or Bilirubin≥1 mg/dl]** can still be advantageous if used in the population suspected with vitamin B12 deficiency as the PPV of the test is set to increase with increasing prevalence.[12]These factors argue for applicability of these parameters **[MCV≥95 fl or MCH≥30 pg or PLT≤1.4 lakh/µl or Bilirubin≥1 mg/dl]** in combination as a screening tool for vitamin B12 deficiency in clinical practice.

In this case, the patient who presents with a value of MCV≥95fl or MCH≥30 pg or PLT≤1.4 lakh/µl or Bilirubin≥1 mg/dl should be considered for further evaluation of vitamin B12 deficiency by conventional methods or for treatment with vitamin B12 supplementation.

This provides tremendous advantage, because for this group, costly investigations like serum homocysteine or MMA can be considered as alternate options.

Limitations

- Along with vitamin B12 deficiency the spectrum of etiologies associated with macrocytic anemia includes folate deficiency, drugs (hydroxyurea, methotrexate, zidovudine, azathioprine, antiretroviral agents, valproic acid, and phenytoin), primary bone marrow disorders (e.g., myelodysplasia and leukemia) and other chronic illnesses like liver disease, hypothyroidism etc.[18] Though the prevalence of these confounding factors in the study population could be predicted as small, their interference with the results cannot be excluded.

- Only total bilirubin was measured in the study
- Hospital population may not be representative of the general population
- Influence of age and gender on red cell indices were not considered in the study

Conclusion

The proposed combinations **[MCV≥95 fl or MCH≥30 pg or PLT≤1.4 lakh/µl or Bilirubin≥1 mg/dl] or [MCV≥95 fl or MCH≥30 pg or PLT ≤1.4 lakh/µl]**used as screening tests has potential for wide application considering its simplicity and advantage of mostly being dependent on the parameters that are obtainable from simple or automatic cell counters, except for serum bilirubin. Hence, it can be used as a potential screening test for choosing patients for further confirmatory laboratory tests for vitamin B12 deficiency resulting in high yield of positive results. This could assist physicians in making correct diagnosis and avoid unnecessary treatment.

This would result in a significant decrease in health cost burden and is especially advantageous in developing country like India and also in underdeveloped countries with limited financial resources.

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