Probability Predicting Tool for Identifying Incidence and Severity of Pancytopenia as a Result of Megaloblastic Anemia

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Abstract: *Background:* One of the most common etiology in the diagnosis of pancytopenia in physician practice is megaloblastic anemia. However there is significant confusion associated with marrow megaloblastic features, which need not always because of pancytopenia. They may be just co-incidental findings. Its often difficult to establish that the peripheral pancytopenia is related to marrow megaloblastic features, as Vitamin B12 and folate are often normal in these cases [because of prior treatment]

Aim: This study was conducted to develop a probability predicting system for possible incidence and severity of pancytopenia as a result of megaloblastic anemia.

Materials and Methods: This is a retrospective analysis conducted at a tertiary care center with approximately 2,000 new cases of megaloblastic anemia. We Hypothesized age, duration of symptoms, Mean Corpuscular Volume [MCV], nutritional status, B12 and folate levels, underlying illness and response to therapy as possible factors associated with pancytopenia of megaloblastic anemia. Receiver operating characteristic (ROC) curves were drawn to predict the cutoff values for risk factors, and a final scoring system was developed with sensitivity and specificity data.

Results: A total of 458 patients with pancytopenia and marrow findings of megaloblastic anemia were analyzed. Based on ROC analysis, following cutoff values were selected: age > 40 years or <20, Folate <30% lower limit, B12 any value close to lower limit of reference laboratory value, Mean Corpuscular Volume>110 fl, duration of symptoms more than 18 weeks, Serum Albumin <2.5 gm/dl [taken as marker for nutrition]. The remaining factors were indicated as present or absent. A score of 1 was assigned for the above factors if they were present. For patients, the final score of 2 or less there is 22% probability of having pancytopenia while patients having score of 6 or more have 89% probability. Similarly when the Mean Corpuscular Volume recovered/reduced by 8 fl at week 3, patients have positive predictable recovery pattern. Those who does not have such recovery by week 3, the etiology of pancytopenia is unlikely to be megaloblastic anemia. And they need further evaluation

Conclusion: The current tool is fairly accurate in predicting development of pancytopenia in patients with low B12 and folate/megaloblastic anemia. This will further help clinicians to look for other reasons of pancytopenia in case, where MCV does not recover beyond week 3 of therapy, so that valuable time of patient is not lost in resource constraints nations like India.

Keywords: Anemia, pancytopenia, Megaloblastic anemia, India, Vitamin B12.

INTRODUCTION

Pancytopenia is an important entity encountered in clinical practice. The clinical definition is the simultaneous presence of anemia, leucopenia and thrombocytopenia. Therefore it exists when Hemoglobin (Hb) is less then 13.5g/dl in males or 11.5g/dl in females; the leucocytes count of less then $4x10^3$/l and the platelets count of less than $150x10^3$/l. [1] There are varying trends in its clinical pattern, etiology, treatment and outcome. The severity and etiology of this clinico- pathological condition determine the management and prognosis of the patients. Among the top causes, megaloblastic anemia is considered commonest in major studies done from this subcontinent ranging from 24-76% of all etiologies. [1-10] The Vitamin B12 and Folate deficiencies in their mild form often may go undetected and it becomes apparent only during times of stress or increased demand. However once it is in its severest forms, the picture of megaloblastic anemia is varied and often confusing. The commonest dilemma for physician is - when to do a bone marrow in presence of megaloblastic peripheral picture?. As megaloblastic anemia responds readily with therapy, the question of postponement of doing a marrow is not scientifically answered yet. Here we proposed one model, which predicts that the probable cause of Pancytopenia is megaloblastic anemia based on few lab parameters and clinical characters. The model predicts both the risk for development of pancytopenia in cases of megaloblastic anemia as well.

METHODS

This is a retrospective analysis conducted at a tertiary care center with approximately 2,000 new cases of megaloblastic anemia. A total of 458 patients

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with pancytopenia and marrow findings of megaloblastic anemia were analyzed. In view of this being retrospective analysis, no eligibility criteria was used and only those cases with complete clinical details were chosen for analysis. We Hypothesized age, duration of symptoms, Mean Corpuscular Volume, nutritional status, B12 and folate levels, underlying illness and response to therapy as possible factors associated with pancytopenia of megaloblastic anemia. Receiver operating characteristic (ROC) curves were drawn to predict the cutoff values for risk factors, and a final scoring system was developed with sensitivity and specificity data. Medical version 7.0 for Windows (MedCalc Software, Mariakerke, Belgium) was used for the analysis. Risk of age was assessed by 5-year interval for age, for B12 and folic acid at 10% lesser value from the highest value of the normal, MCV at 5 Units interval, 0.5 gm/dL intervals for albumin levels, duration of symptoms at 2 weekly interval. For comorbid conditions, as present or absent and assigned a score of 1 and 0, respectively. For all the remaining parameters values above cutoff were scored as 1 and values below cutoff were scored as indicated by ROC curves. Sensitivity and specificity for the final score were assessed for each score level, and based on the percentage of patients experiencing pancytopenia; they were grouped into low-, intermediate-, and high-risk groups.

A total of 458 patients with pancytopenia and marrow findings of megaloblastic anemia were analyzed. Based on ROC analysis, the following cutoff values were selected: age > 40 years or <20, Folate <30% lower limit, B12 any value close to lower limit of reference lab, MCV>110, duration of symptoms more than 18 weeks, Albumin value <2.5 (Figure **1**). The remaining factors were indicated as present or absent. A score of 1 was assigned for the above risk factors. After the scoring system, the categories were chosen again by using the ROC curves and scores of 2 or less, and 6 or above predicted the differences in the incidence of pancytopenia with megaloblastic anemia. For patients, the final score of 2 or less there is 22% probability of having pancytopenia while patients having score of 6 or more have 89% probability. Similarly when the Mean Corpuscular Volume recovered/reduced by 8 fl at week 3, patients have positive predictable recovery pattern. Those who does not have such recovery by week 3, the etiology of pancytopenia is unlikely to be megaloblastic anemia. And they need further evaluation

DISCUSSION

The diagnosis of megaloblastic anemia in our study was established by characteristic peripheral picture, Vitamin B12 levels, folate levels as well as bone marrow findings. The high prevalence of nutritional anemia in India has been cited for the increased frequency of megaloblastic anemia. Because of geographical and social similarities, nutritional anemia may also be responsible for increased frequency of megaloblastic anemia, with Vitamin B12 deficiency being more prevalent than folate deficiency in people with vegetarianism.

Since the closest differential diagnosis of this condition is aplastic anemia and both may have

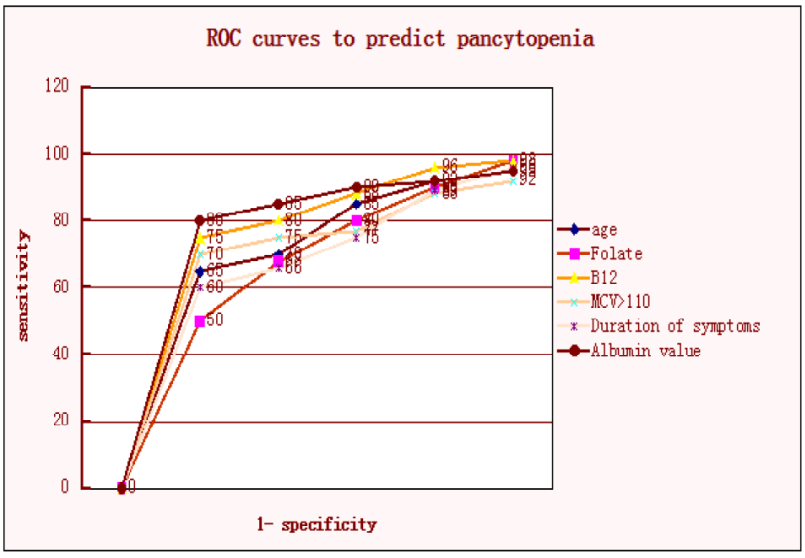

Figure 1: ROC curve for the hypothesize risk factors Results.

presence of macrocytes in peripheral smear examination, it pose a difficulty in distinction between the two in the absence of macro-ovalocytes and hyper segmented neutrophils [11, 12]. Evidence in previous studies suggests that myeloperoxidase index measurement may assist differentiation of megaloblastic from aplastic anemia [13]

The etiology and pathogenesis of this heterogeneous group of disorders under “megaloblastic anemia”share common characteristics: like

- Large cells with an arrest in nuclear maturation.
- Nuclear maturation is immature relative to cytoplasmic maturity.
- Hence, these cells that can be seen in bone marrow aspirates and in peripheral smears have been called megaloblasts.

These abnormalities are due to impaired DNA synthesis and, to a lesser extent, RNA and protein synthesis. Expectedly, these changes are most apparent in rapidly dividing cells such as blood cells and gastrointestinal cells. However, these are not limited to the above and WBC series like hypersegmented neutrophils can be seen on peripheral smears and giant bands occur in bone marrow with platelet morphological alterations. The clinical course could be acute or chronic and can have varied spectrum of severe anemia, pancytopenia, gastrointestinal dysfunction, gloss it is, personality changes, psychosis, and neurological disorders. [14-16]

In the present study patients had a mean age of 34 years and majority were females, which is in agreement with the national trends, where most of the cases are diagnosed in the middle age. The relatively lower incidence of comorbid conditions is due to age distribution (only 20% [44 patients] of the study population is above 45 years, which is the median age for development of diabetes in Indian population). Although literature suggest elevated levels of lactate dehydrogenase (LDH) and indirect bilirubin should fall rapidly [within 2 weeks] and a prolonged elevation of the LDH level indicates a failure of therapy, development of iron deficiency, or an error in diagnosis, the present study suggest that Indians may take longer time for recovery [3-4 weeks] and physicians should wait for the same. Reticulocytosis should be evident within 3-5 days and peaks in 4-10 days. Leukocyte and platelets counts are usually restored to normal within days after therapy has been started, but hypersegmented neutrophils may persist for 10-14 days, which again are bit delayed in the studies population. The hemoglobin should rise approximately 1 g/dL each week. This rise is valuable for monitoring a complete response. If the hemoglobin does not rise appropriately and is not normal within 2 months, other causes of anemia, such as iron deficiency, should be considered. Overall for patients, the final score of 2 or less there is 22% probability of having pancytopenia while patients having score of 6 or more have 89% probability. Similarly when the Mean Corpuscular Volume recovered/reduced by 8 fl at week 3, patients have positive predictable recovery pattern. Those who does not have such recovery by week 3, the etiology of pancytopenia is unlikely to be megaloblastic anemia. And they need further evaluation

CONCLUSION

The current tool is fairly accurate in predicting development of pancytopenia in patients with low B12 and folate/megaloblastic anemia. This will further help clinicians to look for other reasons of pancytopenia in case MCV doesn't recover on week 3, so that valuable time of patient is not lost in resource constraints nations like India.

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