

## A PROSPECTIVE STUDY OF ETIOLOGY OF PANCYTOPENIAS IN TERTIARY CARE HOSPITAL

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### Abstract

**Background:** Peripheral pancytopenia is not a disease by itself; rather it describes simultaneous presence of anemia, leucopenia and thrombocytopenia resulting from a number of disease processes. The aim of this study was carried out to investigate for and to identify the causes of pancytopenia, to find out the frequency of different causes, to determine the incidence of pancytopenia in relation to sex and age and to compare our findings with those of other similar studies from this part of the world. **Materials and Methods:** This Prospective Observational study was done from June 2021 to April 2022 in tertiary care hospital. A total of 100 cases male and female were studied based on inclusion and exclusion criteria. All patients were done routine investigations, like cbp, peripheral smear. further evaluated for the cause of pancytopenia by doing a biopsy. all patients above 5 years were enrolled in the study. The study was carried out in all patients fulfilling the inclusion and exclusion criteria. **Result:** In our study there was male preponderance with males 53 and females 47 in the ratio 1.12:1. there were more number of patients in the age group 41-60yrs[36];21-40yrs[28];5-20yrs[24];61-80yrs[12]; the most common aetiology for pancytopenia was megaloblastic anaemia[53], infectious causes 12. out of infectious causes 4 were SLE, 5 were HIV and 3 were dengue. The next in the order were aplastic anaemia 10, carcinomas 10, fanconi's anaemia 5, MDS 5 and CLD 5. organomegaly was observed in 25 patients with infectious causes and there was no organomegaly in 75 patients. **Conclusion:** We conclude from our study that pancytopenias should be evaluated further for etiology. the diagnosis of etiology of pancytopenia can be achieved by careful physical examination and doing blood investigations. in our study megaloblastic anaemia was the major factor causing pancytopenia.

## INTRODUCTION

Pancytopenia is an important hematological problem encountered in our day-to-day clinical practice. It is a decrease in all three cellular elements of peripheral blood leading to anemia, leucopenia and thrombocytopenia. It exists when the hemoglobin (Hb) level (less than 13.5 g/dL in males or 11.5 g/dL in females), the leucocytes count (less than  $4 \times 10^3 /L$ ) and the platelets count (less than  $150 \times 10^3 /L$ ) are below the specified level. Pancytopenia may arise due to a number of disease processes that vary according to population, age, nutritional status, and the prevalence of infections. Pancytopenia is a common hematological condition of varied etiology. Pancytopenia usually presents with symptoms of bone marrow failure such as pallor, dyspnea, bleeding, bruising and increased tendency to infections. The incidence of various disorders

causing pancytopenia varies according to geographical distribution and genetic mutations. It can result from either failure of production of hematopoietic progenitors in bone marrow, or malignant cell infiltration, or antibody-mediated bone marrow suppression, or ineffective hematopoiesis and dysplasia, or peripheral sequestration of blood cells in overactive reticuloendothelial system.<sup>[1]</sup> The main causes of pancytopenia are aplastic anemia, hypersplenism, myelodysplastic syndrome, nutritional deficiencies leading to megaloblastic anemia, sub-leukemic (acute) leukemias, multiple myeloma, paroxysmal nocturnal hemoglobinuria and infections such as HIV, miliary tuberculosis, brucellosis, and leishmaniasis.<sup>[2]</sup>

Pancytopenia is not a disease entity but a triad of findings that may result from various disease processes, primarily or secondarily involving the

bone marrow. Bone marrow aspiration and biopsy evaluation along with good clinical correlation are of utmost importance to evaluate the causes of pancytopenia and plan further investigations. Pancytopenia is a common hematological problem with an extensive differential diagnosis, and the optimal diagnostic approach to pancytopenia remains undefined. Pancytopenia can result from damage to bone marrow evidenced by low reticulocyte count, or increased destruction of preformed blood cells peripherally with increased reticulocyte count.<sup>[3]</sup> These disorders may affect bone marrow either primarily or secondarily, resulting in the manifestation of pancytopenia.<sup>[4]</sup>

Alterations in peripheral blood counts resulting in bicytopenia or pancytopenia are commonly encountered in paediatric practice. Etiological spectrum in children ranges from common condition like iron deficiency anemia to relatively rare congenital disorders like Fanconi's anemia. It is relatively different in the developing countries from the developed ones. Primary or genetic causes include Fanconi's anemia, dyskeratosis congenita, Swachman's diamond syndrome, and amegakaryocytic thrombocytopenia.<sup>[5]</sup> Acquired causes can be idiopathic or secondary to exposure to radiation, drugs and chemicals (chemotherapy, chloramphenicol, sulfa group, antiepileptic, gold etc), viral infection (cytomegalovirus, Epstein-Barr, hepatitis B or C, HIV etc.), auto-immune, paroxysmal nocturnal hemoglobinuria, and marrow replacement disorders (leukemia, myelodysplasia, myelofibrosis). Frequency may vary from 0.8% to 1.2% to 12.6%.<sup>[6]</sup> Megaloblastic anemia and infections such as enteric fever malaria, kala-azar and bacterial infections can be common causes of pancytopenia in the developing countries.<sup>[7]</sup> Nutritional megaloblastic anemia is also one of the leading causes of pancytopenia in younger children.<sup>[8]</sup>

Hematological complications in brucellosis are common and can be multi-factorial due to the pathogen's tropism for central (bone marrow) and peripheral (spleen) organs of the reticuloendothelial system (RES). Pancytopenia, although mainly reported in adults has also been described in children with brucellosis.<sup>[9]</sup> Folate deficiency is more common in children, while B12 deficiency is more common in adults. It is a common problem in the developing countries.<sup>[10]</sup> A possible explanation of folate deficiency in our country could be the various chronic inflammatory disorders of the gut like chronic diarrheas and malabsorptive states apart from.<sup>[11]</sup> Initially, mild impairment in marrow function may go undetected and pancytopenia may become apparent only during times of stress or increased demand (e.g., bleeding or infection). Megaloblastic anemia has been found to be the most common cause of Pancytopenia worldwide.

Main causes of pancytopenia in our country are megaloblastic anaemia due to nutritional deficiencies, hypersplenism (congestive

splenomegaly, malaria, and leishmaniasis), aplastic anaemia, myelodysplastic syndrome, subleukaemic leukaemias, military tuberculosis, multiple myeloma, paroxysmal nocturnal haemoglobinuria.<sup>[12]</sup>

Megaloblastic anemia and aplastic anemia are important causes of pancytopenia in India.

Megaloblastic anemia: Megaloblastic anemia is a group of disorder characterized by defective nuclear maturation caused by impaired DNA synthesis. This was the most common cause of pancytopenia in India. In India poor eating habits, poverty, poor quality of foods, lack of education and self avoidance of necessary foods may be causes of nutritional deficiency which leading to megaloblastic anemia. The breast-fed infant of a vitamin B12-deficient mother is also at risk of developing severe developmental abnormalities, growth failure, and anemia. Dietary deficiency of vitamin B12 due to vegetarianism is increasing and also causes hyperhomocysteinemia. Elevated methylmalonic acid and/or total homocysteine have been found to be sensitive markers of vitamin B12-deficient diets.<sup>[13]</sup> Since B12 deficiency is the most common cause in adults for pancytopenia, looking upon its causes it has a broad spectrum of etiology such as inadequate dietary intake, impaired absorption in the setting of either intrinsic factor deficiency (pernicious anemia) and/or generalized malabsorption syndromes such as Crohn's disease, intestinal infestation by the fish tapeworm *Diphyllobothrium*, ileal resection and hereditary causes such as severe MTHFR deficiency, homocystinuria, and transcobalamin deficiency.

Aplastic anemia: Aplastic anemia - Aplastic anaemia is defined as pancytopenia with hypocellular marrow in absence of abnormal infiltrate or increased fibrosis. It is a normocytic normochromic anaemia that results from a loss of blood cell precursors, causing hypoplasia of bone marrow leading to pancytopenia. The hallmarks of the disease are pancytopenia and a hypocellular bone marrow. Most cases of aplastic anaemia are acquired and T-cell mediated autoimmune disease. Triggering factors may include drugs, viruses, and toxins but most cases are idiopathic.

Hypersplenism: hypersplenism is an overactive spleen. If spleen is overactive, it remove the blood cells too early and too quickly. There are many condition in which splenomegaly occurs and it lead to hypersplenism with pancytopenia.

Such pancytopenia develop due to premature destruction of RBCs and hemolysis. Causes can be congestive splenomegaly (cirrhosis, congestive heart failure), malaria, hyperreactive malarial splenomegaly, leishmaniasis, thalassaemia, and Hodgkin's disease. Hypersplenism can rarely be idiopathic.

#### **Leukemias**

Hematopoietic neoplasms can present with pancytopenia in both children and adults, and acute leukemias are among the most common of these.

Myelodysplastic syndromes (MDS) are the common haematological diseases characterized by cytopenias associated with abnormal appearing cellular marrow producing ineffective red blood cells.

#### Infections and Autoimmune Disease

most commonly associated with HIV infection. Hepatitis B&C, Epstein barr virus cytomegalovirus, and rarely hepatitis A and dengue virus can also cause pancytopenia. Typhoid and malaria were common infections identified. Bone marrow was hypercellular in malaria but hypocellular in enteric fever. Infections cause bone marrow necrosis and bone marrow suppression along with increased peripheral destruction due to persistent congestive splenomegaly.

Haematologic abnormalities such as anaemia, leucopenia, and thrombocytopenia secondary to peripheral destruction are commonly seen in SLE.

Idiopathic cytopenia of undetermined significance (ICUS) is a recently proposed provisional diagnosis that recognizes patients who present with cytopenias of undetermined aetiology. Diagnostic criteria for ICUS include: i) persistent cytopenia for 6 months (Hb < 11mg/ dl, neutrophil < 1.5x10<sup>9</sup> /L, and platelets < 100x10<sup>9</sup> /L); ii) No morphologic feature of myelodysplasia; iii) normal chromosome analysis; and iv) A detailed clinical history and investigation that excludes other secondary causes of cytopenias

Drugs, which are used in the treatment of rheumatic diseases cause pancytopenia as a side effect or as primary illness.<sup>[14]</sup> In fact, drugs and acute respiratory tract infections caused by viruses (influenza virus, parainfluenza virus, adenovirus, etc.) are very common in cases who are admitted to internal diseases and infectious diseases wards with pancytopenia, but those cases generally recover within a short time. Gaucher disease and sarcoidosis are rarely observed in the etiology of pancytopenia. Common drugs causing pancytopenia are as follows

By bone marrow suppression: Cytotoxic drugs  
b. By dose dependent effect: Chloramphenicol  
c. By immune mediated idiosyncratic reaction NSAIDS, chlormphenicol, sulphonamide, phenothiazines, thiazides, anti-thyroid drugs, anti-epileptics, anti- diabetic drugs, colchicine, azathioprine

Fanconi's anaemia is an autosomal recessive disorder and manifests as congenital developmental anomaly, progressive pancytopenia, and an increased risk of malignancy patients with pancytopenia having the etiologies of aplastic anemia, acute leukemia, and myelodysplastic syndrome have more chances of bleeding manifestation as compared to pancytopenia caused by megaloblastic anemia, kala-azar, or hypersplenism.

Bonemarrow biopsy plays a significant role in understanding the aetiology of pancytopenia in patients.

## MATERIALS AND METHODS

The present Prospective observational study was done in Department of general medicine in tertiary care hospital from June 2021 to April 2022. Patients on myelotoxic chemotherapy were excluded. Two milliliters of EDTA (ethylene diamine tetra-acetic acid) anticoagulated blood were collected and processed through ABX MICROS 60 automated hematology analyzer; and 9 hematological parameters were obtained, which included hemoglobin, red blood cell count, total leukocyte count, differential leukocyte count, platelet count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), packed cell volume (PCV). Erythrocyte sedimentation rate (ESR) was estimated in all cases by Westergren's method. Peripheral smear was stained by Leishman stain for all the cases and examined in detail. Bone marrow aspiration was subsequently carried out under aseptic precaution after obtaining written consent from the patient or guardian.

#### Inclusion Criteria

1. Patients in all age groups and both sexes were included
2. Based on clinical features and supported by laboratory evidence, which included peripheral blood counts for hemoglobin, leukocytes and platelets.
  - 1) Hemoglobin (Hb.) level – below 13.5 g/L for males and below 11.5 g/L for females.
  - 2) Total Leucocyte Count (TLC) - below 4 × 10<sup>9</sup>/L.3) Platelet (Plt.) count – below 150 × 10<sup>9</sup>/L.

#### Exclusion Criteria

1. Patients on chemotherapy

The statistical software SPASS was used to analyse the data and Microsoft word and excel have been used to generate graphs, figure etc.

## RESULTS

In [Figure 1] there is a depiction of male preponderance with males 53 vs females 47 in the ratio F:M [1:1.12]

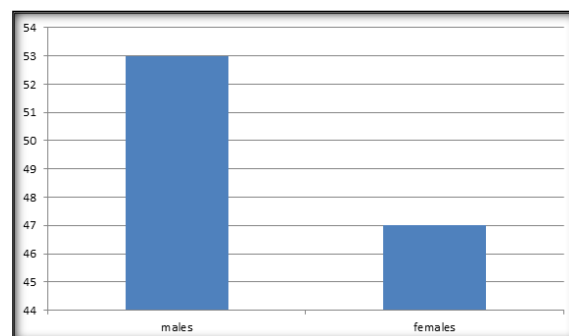


Figure 1: Gender Distribution

In [Figure 2] the pancytopenia patients were more in the age group 41-60yrs followed by patients in the age group between 21-40 years.

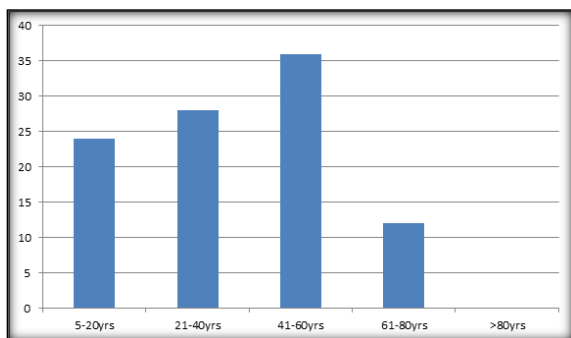


Figure 2: Age Group

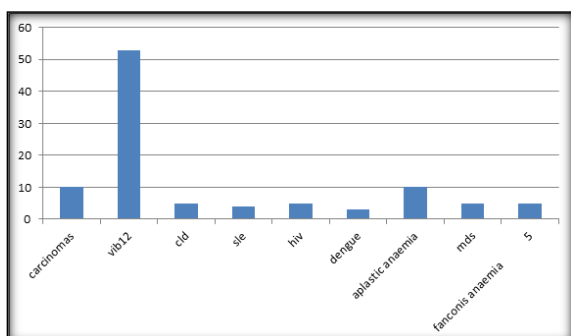


Figure 3:

In [Figure 3] the patients aetiology of pancytopenias is depicted.

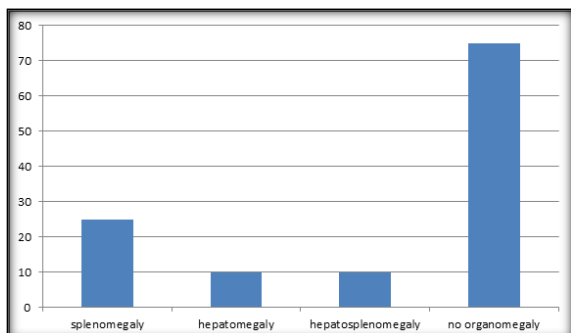


Figure 4:

In [Figure 4] the patients with organomegaly were depicted.

## DISCUSSION

In our study there was male preponderance in the ratio of 1.12:1 in accordance with Satyanarayana et al<sup>14</sup> where there was male preponderance in the ratio of 1.2:1. In our study there were more patients in the age group 40-60 yrs [36] followed by 21-40yrs [28], 5-20yrs [24], 61-80yrs.<sup>[12]</sup> These results were in accordance with Satyanarayana et al,<sup>[14]</sup> where mean age of presentation was 41yrs. In our study there were 20 paediatric patients in accordance with Satyanarayana et al,<sup>[14]</sup> where they were 31. In our study vit b12 deficiency was the

cause in 53[53%] in accordance with Satyanarayana et al,<sup>[14]</sup> where it was 74%. Incidence of 72% was reported by Khunger JM et al.; and 68%, by Tilak V et al.<sup>[15-17]</sup> All the above studies have been done in India, and they stress the importance of megaloblastic anemia being the major cause of pancytopenia. It is a rapidly correctable disorder and should be promptly notified.<sup>[17]</sup> Although bone marrow aspiration studies are uncommon in suspected cases of megaloblastic anemia, if the diagnosis does not appear straightforward or if the patient requires urgent treatment and hematological assays are not available, bone marrow aspiration is indicated. As facilities for estimating folic acid and vitamin B12 levels are not routinely available in most centers in India, the exact deficiency is usually not identified.<sup>[16]</sup> Further in our study aetiological causes were carcinomas 10[10%], CLD 5[5%], infectious 12[12%], aplastic anaemia 10[10%], MDS 5[5%], fanconi's anaemia 5[5%]. Out of infectious causes 4 sle, 5 HIV and 3 dengue were noted. Further in our SUD we noted splenomegaly in 25 patients.

## CONCLUSION

Pancytopenia is not an uncommon hematological problem encountered in clinical practice and should be suspected on clinical grounds when a patient presents with unexplained anemia, prolonged fever and tendency to bleed. The present study concludes that detailed primary hematological investigations along with bone marrow aspiration in cytopenic patients are helpful for understanding the disease process; to diagnose, or to rule out the causes of, cytopenia; and in planning further investigations and management of cytopenic patients. Severe pancytopenia has significant relation with the clinical outcome and can be used as a prognostic indicator. Further emphasis on proper diet may reduce the incidence of pancytopenias in people.

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