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AN OBSERVATIONAL STUDY TO ASSESS THE CLINICAL PROFILES AND ETIOLOGICAL DETERMINANTS IN BICYTOPENIC PATIENTS

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Abstract

Background: Blood is a vital and miraculous fluid apart from water that hosts a myriad of properties and functions that improves the overall well-being, nature and health of an individual. It is made up of erythrocytes, leucocytes, platelets and plasma that provides thermoregulation and stability to maintain various systems of the human body. Reduction of either one of the component is an indirect reflection of failing body system. One such unexplored facet is, Bicytopenia (i.e.) a reduction of erythrocytes and leukocytes in the peripheral blood. With the objective , to investigate the clinical and hematological profiles of patients with Bicytopenia and to identify its underlying etiologies. The following study was performed.

Methods: Using simple random sampling method, 150 patients were randomly selected for the study. Patients presenting with bicytopenia at over a 6 month period from admitted to Saveetha medical college and hospitals, Chennai were taken up for the study. Comprehensive clinical assessments, including detailed history, physical examination, laboratory investigations, and bone marrow evaluations when indicated, were performed. Data collected, recorded and analyzed.

Results: All ages were found to have bicytopenia, with a mean age of 31.5 years. Bicytopenia was present in Infants (< 2 years)9.12%, Children (2–12 years)7.24%, Adolescents(13–18)8.00%, Adults (19–60)63.40% and Elderly (> 61 years)12.24%. mean age was 31.5 years. Out of (n-150),60%(90)presented with fatigue as major complaint. Anemia with leukopenia (25%) and leukopenia with thrombocytopenia (12%) were the two bicytopenias that were seen most frequently.66.6% men presented with bicytopenia when compared to women. Bicytopenia was shown to have non-malignant (55%) as its most frequent etiology, followed by infectious (31.6%), malignant (8.2%), and drug-induced (3%). In the non-malignant group, immune thrombocytopenic purpura, alcoholic liver disease, and megaloblastic anemia were the most common etiologies. Dengue (11% of all infectious diseases) was the most prevalent. The hematological malignancies were most substantially linked with symptoms such lymphadenopathy, splenomegaly, and hepatomegaly ($P \leq 0.005$). The most prevalent non-malignant symptoms were pallor, hemorrhage, hepatomegaly, and splenomegaly ($p < 0.005$).
In the infectious category, fever and lymphadenopathy were most prevalent ($p < 0.005$).
Lymphadenopathy, hepatomegaly, and splenomegaly were the most prominent symptoms in drug induced etiology ($P < 0.005$).

Conclusion: Due to the diverse etiological spectrum of bicytopenia, malignancies and non-malignancies can be detected in time. Thereby, a tailored diagnostic approach and treatment incorporating clinical evaluation and targeted investigations for effective management can be designed easily

Keywords: Anemia, Leukopenia, Thrombocytopenia, Bicytopenia, and Leukaemia.

INTRODUCTION

Water is considered as the elixir of life whereas blood is the elixir of living. It is a complex tissue composed of red blood cells, white blood cells, platelets, and plasma. From cellular metabolism to orchestrating the body's defense mechanisms, blood is indispensable for maintaining homeostasis and overall vitality [1]. William Harvey's discovery laid the foundation of modern principles that explained the various facts and factuality regarding this body fluid [2].
Time and ages various ailments related to blood cell disorders such as aplasia, malignancies, non-malignancies, decreased blood counts, increased blood counts, pancytopenia have been thoroughly studied. But, the intermediate stage Bicytopenia is a concept that needs to be explored in detail to screen faster the malignant and non-malignant conditions.
Bicytopenia is defined as the simultaneous reduction of two of the three major cellular elements in peripheral blood i.e. erthrocytes, leucocytes, or thrombocytes. Although detected lesser than pancytopenia, bicytopenia remains a red flag in clinical practice because it often reflects an underlying pathological process in our body that needs attention [3]. The etiological spectrum of bicytopenia is notably broad, encompassing a range of conditions from bone marrow failure syndromes, such as aplastic anemia and myelodysplastic syndromes, to hematological malignancies, nutritional deficiencies, autoimmune disorders, and even extramedullary causes like hypersplenism [4].
The clinical presentation of bicytopenia is highly variable, with many patients manifesting non-specific symptoms such as fatigue, pallor, or increased susceptibility to infections. In other cases, more ominous signs such as fever, bleeding tendencies, or weight loss may herald a malignant process [5]. Comprehending ,the pathogenesis of bicytopenia sheds light on hematopoiesis, immune regulation, and the complex interplay of systemic and local factors causing a major disease. For instance, bone marrow infiltration by malignant cells disrupts normal hematopoietic function, while nutritional deficiencies, commonly involving iron, folate, or vitamin B12, also represent a significant cause [6]. Understanding, the underlying etiology helps in distinguishing between benign and life-threatening causes. In light of these considerations, an approach that integrates clinical findings with advanced diagnostic modalities is essential for optimal patient management.
This study aims to delineate the clinical profiles and etiological determinants of bicytopenia in a cohort of Bicytopenic patients. Thereby, focusing on defining patterns that may guide clinicians in differentiating between various underlying causes in order to develop more personalized diagnostic strategies and effective therapeutic interventions, ensuring that patients receive timely care and also limit the spread of the disease.

METHOD

All study participants provided written informed consent, and the institutional ethics committee approved the use of human volunteers. Of the 200 patients who consented to participate, (n-150) were randomly selected using the lottery method. Each participant underwent a comprehensive evaluation that included recording a detailed history and performing a clinical examination—either using a standardized proforma or through an in-person interview.
Peripheral blood smears were analyzed for cell morphology, platelet counts, and the presence of hemoparasites such as malaria, although it should be noted that Wright's stain discolored the smears. In line with clinical recommendations, bone marrow aspiration and trephine biopsy were performed. Wright's stain was applied to all aspirate smears, while trephine biopsy sections were stained with hematoxylin and eosin (H&E) [5–7]. When needed, additional stains—such as myeloperoxidase, periodic acid–Schiff (PAS), and Perl's stain—were applied to the aspirate smears. All other relevant investigations recorded in the medical records were also noted.
Patients were selected based on the following criteria: only inpatients with bicytopenia were included, while those with pancytopenia or isolated cytopenia were excluded. The study specifically focused on three common combinations of cytopenias:

- Anemia with thrombocytopenia
- Anemia with leukopenia
- Leukopenia with thrombocytopenia

Bicytopenia was defined as a reduction—below the normal range for a given age and sex—in any two blood cell lineages. To determine both the most typical combination of cytopenias and the prevalence of bicytopenia, careful examinations of peripheral smears and blood counts were carried out. Patients presenting with persistent bicytopenia involving two blood cell lines (e.g., anemia and thrombocytopenia) confirmed through repeated complete blood counts and who gave consent to study were included and patients with both bicytopenia and pancytopenia together were excluded from study

The sample size for the study was calculated using a study by Singh A et al [7]. Using the values, p- 55.5% (0.555), d- 10% (0.10), and a confidence level of 95% (Z=1.96).

$n=Z^2\times p\times(1-p)/d^2$

$=(1.96)^2\times0.555\times(1-0.555)(0.10)^2$

≈94.9 (**95 patients**)

Adjusting for a potential 10% nonresponse rate, final sample size: **106 patients**

Total of 150 patients were selected for the study.

The underlying causes of bicytopenia were categorized into four major groups: infectious, drug-induced, malignant, and nonmalignant. Hematological malignancies associated with bicytopenia were classified under the malignant group. Nonmalignant disorders, except those resulting from active infections or drug-induced causes, were grouped as nonmalignant. Cases with active infections, confirmed by serological tests, were placed in the infectious category, and instances of bicytopenia occurring after therapy were considered drug-induced.

Finally, the study assessed five key clinical findings, which included pallor, hepatomegaly, lymphadenopathy, and splenomegaly.

Statistical Analysis

The clinico-hematological profiles of patients with bicytopenia were analyzed using descriptive statistics, including measures such as mean, standard deviation, and percentage. Comparisons of categorical variables were performed using the Chi-square test, with statistical significance determined at a probability (pp) value of less than 0.04. Data analysis was conducted using SPSS (IBM, USA) and Microsoft Excel (Microsoft, USA).

RESULTS

The collected data were tallied and examined. Five age groups were watched and analyzed for bicytopenia: infants under 2 years old (9.33%); children aged 2 to 12 years (8%); adolescents aged 13 to 18 (10.66%); adults aged 19 to 60 (60%); and people over 61 years old (12%). With a range of 1 day to 80 years, the mean age was 34.6 years. Males made up 66.2% of the cases, and females made up 33.8%, according to the gender distribution. (Table 1)

Age Group	Percentage (%)	Number of Cases (n)	Mean ± SD
Infants (< 2 years)	9.33	14	
Children (2–12 years)	8.00	12	
Adolescents (13–18)	10.66	16	**34.65±19.39**
Adults (19–60)	60.0	90	
Elderly (> 61 years)	12	18	
Total	100.00	**150**	

Table 1 Shows Distribution of Bicytopenia Patients according to different Age Groups

The most frequent bicytopenia was found to be anemia with thrombocytopenia (106 cases, 70.6%),followed by anemia with leukopenia (41 cases, 27.33%) (Table 2).

Out of 106 anemia with thrombocytopenia cases, 52 (34.66%) of non-malignancy causes were the highest cause for bicytopenia, followed by 30 (20%)infectious causes and 17 (11.33%) malignant causes. (Table 2)

Bicytopenia Combination (n-150)	Malignant n (%)	Nonmalignant n (%)	Infectious n (%)	Drug-induced n(%)	Autoimmune n (%)
Anemia with thrombocytopenia	17 (11.33%)	52 (34.66%)	30 (20.0%)	2 (1.33%)	5 (3.3%)
Anemia with leukopenia	14 (9.33%)	9 (6%)	14 (9.33%)	2 (1.33%)	2 (1.33%)
Leukopenia with thrombocytopenia	0 (0.0%)	1 (0.66%)	1 (0.66%)	0 (0.0%)	1 (0.66%)

Table 2 shows the clinical presentations of bicytopenia in various identified causes of Bicytopenia
Pallor was the most prevalent symptom (98%) at the time of presentation. Followed by lethargy (66%),Hepatomegaly (53.3%, splenomegaly (40%) and Anorexia (33.3%). (Table 3)
In hematological malignancies, Anorexia (23.3%), splenomegaly (22%), and hepatomegaly (20.3%) were the most frequent clinical features. The most common symptoms in non-malignant disorders were pallor (88 %),hepatomegaly (25 %), and splenomegaly (8%). In the infectious group, Lethargy (50%) and fever(10 %) were the most prevalent clinical symptoms. Hepatomegaly (8.0%), and splenomegaly(10.0%) were the most common symptoms in drug induced and auto immune disorders. (Table 3)
The level of significance was investigated using the chi-square test. The cause of the cytopenia and the clinical outcome of bicytopenia were statistically significant ($p<0.05$). (Table 3)

Symptom	**Number of Cases (%)**
Fever	15 (10%)
Anorexia	50 (33.3%)
Lethargy	100 (66.6%)
Jaundice	5 (3.33%)
Inadequate dietary history	27 (18%)
Pallor	147 (98%)
Bone pain	5 (3.33%)
Hepatomegaly	80 (53.3%)
Splenomegaly	60 (40%)

Table 3 shows the commonest signs and symptoms seen in bicytopenia patients

Adults form the largest group (n=90), contributing to a dominant proportion of the sample. The highest mean Hb% is observed in **Children (8.8500)**, while the lowest is seen in the **Elderly (8.1167)**. the observed differences between mean Haemoglobin values in all group show significance of ($p<0.005$) thereby proving its statistically significant and accepting the null hypothesis. (Table 4)

Age groups	n-150	Mean (Hb%)	Std. Deviation	F	Sig.
Infants (<2 yrs)	14	8.2929	.27023	3.453	.010
Children (2-12 yrs)	12	8.8500	.43797		
Adolescent (13-18 yrs)	16	8.4750	.69041		
Elderly (>61 yrs)	18	8.1167	.83964		
Adults (19-60 yrs)	90	8.2167	.61649		

Table 4 shows Hemoglobin Levels (Hb%) Across Different Age Groups in Bicytopenic Patients

DISCUSSION

Bicytopenia and Pancytopenia in children are hematological abnormalities with diverse etiologies and clinical presentations. Infections and hematological disorders, including malignancies and bone marrow failure syndromes, are common underlying causes. [5] A comprehensive diagnostic approach involving clinical evaluation and peripheral blood examination, was done in this study for accurate diagnosis and appropriate management.

Demographic Details

This study included a broad age range, from infants to the elderly, with the majority of cases (60%) occurring in adults aged 19 to 60 years, there was a marked male predominance (66.2%). This contrasts with several other studies that specifically focused on pediatric populations, typically defined as children aged 1 month to 12 or 14 years [8] .... For instance, one pediatric study included children aged 1 month to 12 years [8] , while another focused on those aged less than 12 years [9] . A study by Kumar et al [10] excluded children younger than six months or older than 14 years. Khalid N et al [9] included children recorded children aged 12 years of age with majority cases of bicytopenia. Since, our cohort predominantly comprised adults, due to regional variations in referral patterns, nutritional status, or exposure to etiologic factors, adults recorded more number of cases.

Children aged 2 to 12 years constituted 8% of the bicytopenia cases . In contrast, studies focused on pediatrics often report a higher prevalence of cytopenias in this age group. For example, Anand et al [11] noted that most study participants with pancytopenia were in the age group of 1–6 years, and those with bicytopenia were in the 7–12 years age group.

Prevalence of Bicytopenia vs. Pancytopenia:

In the present study, 150 bicytopenic patients were recorded. Sharma et al [12] reported on 26 cases of bicytopenia and 24 cases of pancytopenia in their pediatric study. Similarly, Anand et al [11] included 264 patients with bicytopenia and 36 with pancytopenia. Emphasizing on the fact that bicytopenia cases were more prevalent than pancytopenia cases. Kumar et al [10] also studied both conditions in children, noting a similar trend in the frequencies of etiologies in both groups.

Clinical profile

Anemia with thrombocytopenia was the most common combination in our study (70.6%), followed by anemia with leukopenia (27.33%). Within the anemia with thrombocytopenia group, non-malignant causes were predominant (34.66%), followed by infectious causes (20%) and malignant etiologies (11.33%). These findings are consistent with those reported by Logeshwaran K et al [13] and Kumar et al [10], found infections to be the most common etiology for both bicytopenia and pancytopenia in children, followed by benign hematological disorders, systemic illnesses, and malignancies. This aligns with the findings of Sharma et al [12] where infectious origins were common, particularly sepsis.

However, other studies, particularly those including adults or with different geographical focuses, report different leading causes. For instance, a study by Sharif et al [14] found nutritional deficiency anemias to be the most common cause of bicytopenia across all age groups, while acute lymphoblastic leukemia was common in the pediatric group. The geographical location appears to influence the etiological spectrum, as noted by Anand et al [11] and Patil GR et al [15] where the frequency of malnutrition and regional diseases like malaria and enteric fever shape the causes reported. Dengue was a common infectious etiology in several studies . Thakur et al [16] study in adults reported infectious cases as the most common etiology of bicytopenia , contrasting with Naseem et al.'s [4] findings of malignancy being most common in children with bicytopenia in their study.

Etiological Spectrum:

The overall symptom profile was dominated by pallor (98%), with high incidences of lethargy (66.6%), hepatomegaly (53.3%), and splenomegaly (40%). The predominance of pallor aligns with the central role of anemia in these patients and is comparable to the observations in earlier studies [17] [18]. Notably, the symptom profile varied with etiology—hematological malignancies tended to exhibit anorexia, splenomegaly, and hepatomegaly, whereas infectious causes were more frequently associated with lethargy and fever. This differentiation emphasizes the need for a detailed clinical evaluation to guide subsequent diagnostic work-ups, as similarly advocated by similar studies [19].

Our hematological analysis revealed significant age-related differences in the mean hemoglobin levels ($p < 0.005$). Specifically, children showed the highest mean hemoglobin (8.85 g/dL), while the elderly had the lowest (8.12 g/dL). This observation is in concordance with previous literature that attributes such differences to variations in marrow reserve, nutritional status, and chronic comorbidities in older patients [20] .Additionally, ANOVA analysis demonstrated a significant association between the etiological causes of bicytopenia and clinical outcomes ($p < 0.05$), highlighting that an early, accurate etiological diagnosis is crucial for effective management—a point also emphasized in earlier research [21].

In summary, our study confirms that bicytopenia is a multifactorial condition with variable clinical presentations and etiologies. The high frequency of anemia with thrombocytopenia, significant age-dependent variations in hemoglobin levels, and distinct clinical profiles across etiologies underscore the complexity of bicytopenia. Future studies with larger populations and longitudinal follow-up are warranted to further refine diagnostic algorithms and enhance patient management strategies [20] [21].

CONCLUSION

Bicytopenia, an important hematological finding, serves as a vital diagnostic cue for exploring various hematological illnesses. It helps practitioners manage diverse clinical scenarios effectively by guiding them toward targeted investigations, thereby minimizing unnecessary diagnostic tests.

This condition acts as a clinical marker for numerous benign and malignant disorders. To facilitate rapid evaluation and early diagnosis of patients with bicytopenia, this study systematically categorizes its etiologies and associated symptoms across different age groups in a tabular format. By understanding the underlying causes, healthcare providers can enhance diagnostic accuracy and deliver effective care. In patients with bicytopenia, this approach has the potential to significantly reduce morbidity and mortality.

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