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PANCYTOPENIA: A CLINICO-HEMATOLOGICAL CROSS-SECTIONAL STUDY IN ASMARA, ERITREA

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ABSTRACT

Introduction: Pancytopenia is a hematological phenomenon that is a challenge in clinical practice. This study aimed at describing the clinico-hematological features of pancytopenic patients in the Eritrean setting. **Methodology:** This was a cross- sectional study carried out in the National Health Laboratory and Orotta National Referral and Teaching Hospital, Asmara, Eritrea, from December 2015 to November 2017. Seventy-five patients with pancytopenia were included in the study, for which complete blood count, bone marrow aspiration and trephine biopsies were performed. Clinical and hematologic evaluation was conducted. Data entry and analysis was done using Epi-Info 7, Microsoft Excel and SPSS. **Results:** Out of the 75 cases, there were 49 (65%) adults (age 15 and above) and 26 (35%) children. Males were 41(61%) and females 29 (39%) with male to female ratio of 1.6:1. The median age was 20. The maximum number of patients was in the ages between 15 to 35 years. More than half (56%) of the patients hailed from two zones (Southern and Western regions) of Eritrea. The most common presenting symptoms were fever (80%), generalized body weakness (79%), loss of appetite (55%) and the commonest signs were pallor (93%), splenomegaly (71%) and hepatomegaly (44%). The two most common causes of pancytopenia were found to be hypersplenism (42.7%) and visceral leishmaniasis (29.3%). **Conclusion:** The commonest causes of pancytopenia were hypersplenism and related tropical infections like visceral leishmaniasis followed by Megaloblastic anemia and Aplastic Anemia.

KEYWORDS: Pancytopenia, Hypersplenism, Visceral Leishmaniasis.

INTRODUCTION

Pancytopenia is a hematological phenomenon that is a challenge in clinical practice. It is defined as a decrease in the three lines of blood cells – anemia, leucopenia and thrombocytopenia. The criteria for definition of pancytopenia vary according to age and gender, reflecting the different normal values in each group. A commonly used cutoff in adults is hemoglobin level below 13.5 g/L for males and below 11.5 g/L for females; total leucocyte count below 4×10^9/L; and platelet count below 150×10^9/L.[1] In children the reference ranges that have been used in several studies are hemoglobin <10g/dL, total leucocyte count <4000/mm3 and platelets <100,000/mm3.[2]

Pancytopenia is a triad of hematologic abnormality and not a single disease. The preliminary classification of a patient as pancytopenic, however, facilitates clinical systematic workup of the patient. Pancytopenia evaluation should be systematic in unraveling the underlying disease entity followed by appropriate treatment and follow up of patients. Pancytopenia is a feature of many serious and life threatening diseases. The causes of pancytopenia can be a decrease in hematopoietic cell production, ineffective hematopoiesis or peripheral destruction of cells. The hematopoietic cell production can be suppressed by infections, toxins, malignant cell infiltration, chemotherapies and radiation leading to hypocellular marrow. Dysplasia and peripheral sequestration of blood cells or peripheral destruction of all blood cell lineage can also lead to pancytopenia.[3]

The etiologies of pancytopenia vary widely between different age groups and geographical locations. These include infectious causes, nutritional deficiencies, malignancies and bone marrow failure syndromes.[4] The major causes of pancytopenia in pediatric age groups are classified as inherited and acquired pancytopenia. The causes of inherited pancytopenia include Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis

congenita, congenital amegakaryocytic thrombocytopenia, unclassified bone marrow failure syndrome and other genetic syndromes such as Down syndrome and Noonan syndrome. The acquired pancytopenia are similar to that of adults' etiologic agents including exposure to medications, chemicals, radiations and diseases that are infectious and immune-mediated.[5]

The clinical manifestations of pancytopenia reflect the reduction in the underlying hematologic components as patients present with manifestations of anemia such as fatigue and shortness of breath; thrombocytopenia manifestations such as mucosal bleeding and bruising; and leucopenia manifestations such as recurrent infections and stomatitis.[6]

An exhaustive clinical history, detailed physical examination, complete blood count with reticulocyte count and peripheral blood smear are essential for diagnosis. Bone marrow examination is required to delineate the cause of pancytopenia as it plays a major role in identification of hematological malignancy, unexplained cytopenia and storage disorders. Trephine biopsy is mainly undertaken when hypoplasia or aplasia of bone marrow are suspected on aspiration.[7]

The etiology of pancytopenia varies in different populations studied with differences in age patterns, nutritional status, climate and the prevalence of infections.[8] To our knowledge, there has not been a published study conducted in the area of pancytopenia in the Eritrean population and this study sheds light on the burden of this conundrum in patients seen in Eritrea. To that end, our study elucidated the clinico-hematologic profile of pancytopenic patients in Orotta National Referral and Teaching Hospital and National Health Laboratory (NHL) - the only settings where bone marrow aspiration or biopsy services is done in the country.

METHODS AND MATERIALS

A hospital-based cross-sectional study was conducted by enrolling patients who fulfill the criteria for pancytopenia and sent for complete blood count and bone marrow examination to the National Health laboratory (NHL) from Orotta National Referral and Teaching Hospital, Asmara, Eritrea from December 2015 to November 2017. The research proposal was reviewed by the Ethical Committee of the research unit in the ministry of health and ethical clearance was approved. Patients who fulfilled the inclusion criteria were: (1) all patients whose complete blood counts (CBC) showed pancytopenia according to the operational definition stated above, (2) who underwent bone marrow examination, and (3) who gave informed consent or consent taken from their guardian (pediatric patients). Previously diagnosed pancytopenic cases, patients who received blood transfusions or patients on cytotoxic drugs were excluded. A detailed clinical history and physical examination was performed in the patients who met the inclusion criteria and blood samples were obtained by routine phlebotomy procedure 2.5 ml of EDTA (ethelendiamine tetra-acetic acid) anticoagulated and processed through automated hematology analyzer. All hematological parameters were conducted, which included hemoglobin, red blood cell count, total leukocyte count, differential count, platelet count, and red blood indices.

Bone marrow aspiration was performed from posterior superior iliac spine under aseptic condition. Slides were obtained with routine Leishman stain and examined. All hematologic examinations were done by the lead author - a hematopathologist. Both clinical and hematologic findings were filled to a standardized questionnaire and data fed into Epi-Info software version 7. Data cleaning and analysis were done using Microsoft Excel, Epi-Info and SPSS version 23. Statistical significance was calculated for each parameter using a 95% confidence interval.

RESULTS

Study Population

A total of 75 patients who underwent bone marrow examination for hematologic evaluation of pancytopenia were studied over a period of 24 months. Out of the 75 cases, there were 49 (65%) adults(age 15 and above) and 26 (35%) children. Gender wise, 46 (61%) were males and 29 (39%) were females. The mean age in males was 27 (ranging 1 to 94) with standard deviation of 21 while in females the mean age was 20 (ranging 2 to 56) with standard deviation of 15. The median age was 20; 24.5 in males and 17 in females. The male to female ratio was 1.6:1. The maximum number of patients was in the age range of 15 to 25 (20%) and 25 - 35 (19%) as shown in table 1. The distribution of the patients' address in the six zones of Eritrea was as shown in table 2.

Table 1: Age distribution of the pancytopenia patients who underwent bone marrow.

Age Interval	Number of cases	Percent	95% Confidence Interval	Male (%)	Female (%)
01-05	10	13.33%	6.58% - 23.16%	6 (13.04%)	4 (13.79%)
05-10	11	14.67%	7.56% - 24.73%	6 (13.04%)	5 (17.24%)
10-15	5	6.67%	2.20% - 14.88%	4 (8.70%)	1 (3.45%)
15 – 25	15	20.00%	11.65% - 30.83%	7 (15.22%)	8 (27.59%)
25 – 35	14	18.67%	10.60% - 29.33%	8 (17.39%)	6 (20.69%)
35 – 45	8	10.67%	4.72% - 19.94%	6 (13.04%)	2 (6.90%)
45 – 55	6	8.00%	2.99% - 16.60%	4 (8.70%)	2 (6.90%)
55 – 65	3	4.00%	0.83% - 11.25%	2 (4.35%)	1 (3.45%)
65 – 75	1	1.33%	0.03% - 7.21%	1 (2.17%)	0
75 – 85	1	1.33%	0.03% - 7.21%	1 (2.17%)	0
85 – 95	1	1.33%	0.03% - 7.21%	1 (2.17%)	0
TOTAL	75	100.00%		100.00%	

Table 2: Distribution of the patients' address in the six regions (Zobas) of Eritrea.

Eritrean Region	Number of Cases	Percent	95% Confidence Interval
Southern (Debub)	22	29.33%	19.38% - 40.98%
Gash Barka	20	26.67%	17.11% - 38.14%
Central (Maekel)	14	18.67%	10.60% - 29.33%
Northern Red Sea	12	16.00%	8.55% - 26.28%
Anseba	7	9.33%	3.84% - 18.29%
Southern Red Sea	0	0	0
TOTAL	75	100.00%	

Figure 1: Symptoms of the Pancytopenic Patients

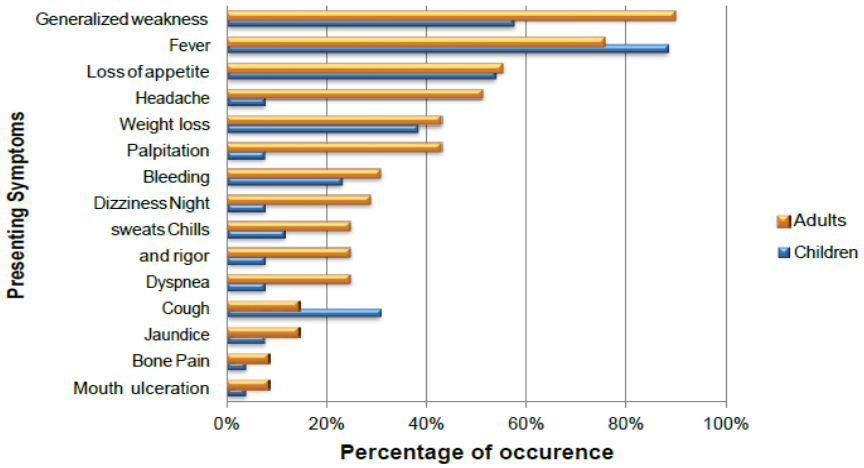
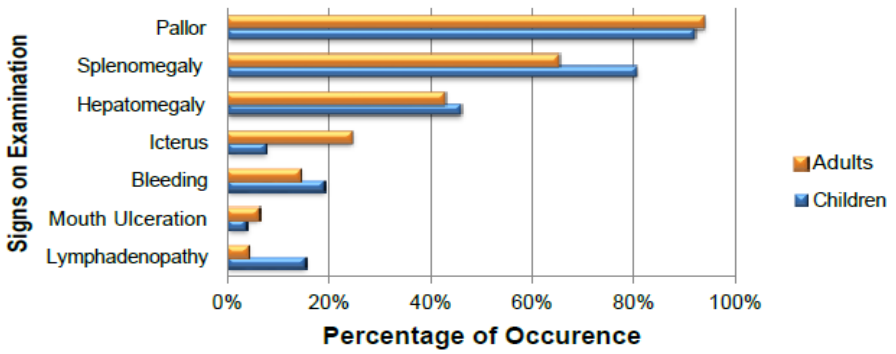


Figure 2: Signs of the Pancytopenic Patients



Clinical Features

Fever was the most common presentation observed in 80% of the cases followed by generalized body weakness (79%) and loss of appetite (55%). The most common physical examination finding was pallor (93%), followed by splenomegaly (71%), and hepatomegaly (44%). Table 3 shows the clinical presentations of the patients. The frequency of the presenting symptoms and signs were slightly different among adults and children. In adults the commonest clinical findings were pallor (94%), generalized weakness (90%), fever (76%) and splenomegaly (65%). In children the commonest findings were fever (89%), generalized weakness (58%), loss of appetite (54%) and weight loss (39%). See figure 1 and 2.

Table 3: History and physical examination findings of the patients.

History	Frequency	Percent
Fever	60	80.00%
Generalized weakness	59	78.67%
Loss of appetite	41	54.67%
Weight Loss	31	41.33%
Headache	27	36.00%
Palpitation	23	30.67%
Bleeding	21	28.00%
Dizziness	16	21.33%
Night Sweats	15	20.00%
Cough	15	20.00%
Chills and Rigor	14	18.67%
Dyspnea	14	18.67%
Jaundice	9	12.00%
Bone Pain	5	6.67%
Mouth Ulceration	5	6.67%
Intake or exposure to chemicals or drugs	0	0.00%
PHYSICAL EXAMINATION		
Pallor	70	93.33%
Splenomegaly	53	70.67%
Hepatomegaly	33	44.00%
Jaundice	14	18.67%
Bleeding	12	16.00%
Lymphadenopathy	6	8.00%
Mouth Ulceration	4	5.33%

Hematologic Features

Complete blood count, peripheral blood smear and bone marrow aspiration were done in all patients. The mean hemoglobin level was 8.05 g/dL (ranging 3.6 to 12.7). The hemoglobin level was >10 g/dL in 7 (9.3%), 8 to 10 g/dL in 33 (44%), 6 to 8 g/dL in 26 (34.7%), and <6 g/dL in 9 (12%) of patients.

The mean WBC count was 2.67 (ranging 0.5 to 3.9 WBCs 10^9/L) and the mean platelet level was 62.33 X 109 (ranging 1 to 131). Nine patients had absolute neutrophil count less than 0.5 (12%).

Peripheral morphology classification of the red blood cells is shown in table 4.

Table 4: Peripheral morphology classification of the red blood cells.

RBC Morphology	Number of Cases	Percent	95% Confidence Interval
Macrocytic Normochromic	13	17.33%	9.57% - 27.81%
Microcytic Hypochromic	15	20.00%	11.65% - 30.83%
Normocytic Normochromic	47	62.67%	50.73% - 73.57%
TOTAL	75	100.00%	

The bone marrow cellularity was hypercellular in 67 (89%), normocellular in 5 (7%), and hypocellular in 3 (4%).

Erythropoiesis was hyperplastic in 66 (88%) and hypoplastic in 9 (12%). Megakaryocytes were increased in 20 (27.4%), normal in 17 (23.3%) and decreased in 36 (49.3%). Excess blasts were seen in four cases, all of which were diagnosed as acute leukemia.

Causes of Pancytopenia

The causes of pancytopenia according to the bone marrow aspiration are shown in table 5. Hypersplenism due to causes other than visceral leishmaniasis topped the list (in 43%) followed by visceral leishmaniasis (29%) and megaloblastic anemia (13%).

Table 5: Distribution of causes of pancytopenia.

Diagnosis	Number of Cases	Percent	95% Confidence Interval	Male (%)	Female (%)
Hypersplenism	32	42.67%	31.31% - 54.62%	22 (47.83%)	10 (34.48%)
Visceral Leishmaniasis	22	29.33%	19.38% - 40.98%	14 (30.43%)	8 (27.59%)
Megaloblastic Anemia	10	13.33%	6.58% - 23.16%	5 (10.87%)	5 (17.24%)
Aplastic Anemia	5	6.67%	2.20% - 14.88%	2 (4.35%)	3 (10.34%)
Acute Lymphoblastic Leukemia	3	4.00%	0.83% - 11.25%	2 (4.35%)	1 (3.45%)
Acute myeloid leukemia	2	2.67%	0.32% - 9.30%	0	2 (6.90%)
Chronic Lymphocytic Leukemia	1	1.33%	0.03% - 7.21%	1 (2.17%)	0
TOTAL	75	100.00%			

The bone marrow was evaluated for parasites. Twenty two cases showed Leishmania Donovani bodies and, thus, the diagnosis of visceral leishmaniasis was confirmed. Only one patient who showed hypersplenism was found to have malaria parasite in the bone marrow.

The diagnosis was stratified by age category (children or adult) as shown in table 6. In adults hypersplenism was the most common cause while in children visceral leishmaniasis was the top in the list.

Table 6: Causes of pancytopenia stratified by age category.

Diagnosis	Number of Cases	Percent	95% Confidence Interval
Adults			
Hypersplenism	22	44.90%	30.67% - 59.77%
Visceral Leishmaniasis	11	22.45%	11.77% - 36.62%
Megaloblastic Anemia	10	20.41%	10.24% - 34.34%
Aplastic Anemia	3	6.12%	1.28% - 16.87%
Acute myeloid leukemia	2	4.08%	0.50% - 13.98%
Chronic Lymphocytic Leukemia	1	2.04%	0.05% - 10.85%
TOTAL	49	100.00%	
Children			
Visceral Leishmaniasis	11	42.31%	23.35% - 63.08%
Hypersplenism	10	38.46%	20.23% - 59.43%
Acute Lymphoblastic Leukemia	3	11.54%	2.45% - 30.15%
Aplastic Anemia	2	7.69%	0.95% - 25.13%
TOTAL	26	100.00%	

DISCUSSION

Pancytopenia is a relatively common hematological presentation in patients seen in general practice, pediatrics and internal medicine. Early recognition of the causes of pancytopenia, although myriad, is of paramount importance. In considering the different pathologies, the epidemiology of the disease is crucial to elucidate the causes of pancytopenia.

Our study sheds light on the demographics, clinical presentations and hematological profile of pancytopenic patients and diseases associated as etiology in the Eritrean setting, where there is paucity of data on the subject. Upon clinical and hematologic evaluation of 75 adult and pediatric pancytopenic patients who underwent bone marrow examination, the salient findings of our study were that males accounted for two third of the cases, hypersplenism and visceral leishmaniasis were the two most common causes both in adults and children, and young adults were most commonly affected.

The age range of our patients were between one year to 94 years with two third of the patients being males and females accounting for a third of the cases with a male to female ratio of 1.6 to 1. Patients who were in pediatric age group also accounted for a third of our study population and the highest number of cases were in the age group of 15 to 25. The mean age at presentation for pancytopenia patients in our study were 27 (median age of 24.5 years) and 20 years (median age of 17 years) in males and females respectively. This was found to be consistent with other studies which showed mean ages to be 20-40 years and males have been predominating with male to female ratio from 2.6 to 1 to 4:1 in most studies indicating male predominance.[7,9,13] In accordance with the studies in other countries, male predominance and younger age group of patients were the demographic characteristics of our pancytopenic patients.

More than half of patients (56%) were from two regions of Eritrea, namely Zoba Debub (Southern region) and Zoba Gash Barka (Western region of Eritrea). These regions are characterized by higher prevalence of tropical diseases such as malaria and visceral leishmaniasis in the country. These regions were the residences for 62.6% of the cases of hypersplenism and 59% of visceral

leishmaniasis our study. These two Zobas also account for high population density and large geographic area compared to other zones in Eritrea, which probably have a role for the high patient burden (56%) out of the six zones.

Clinical Features

The commonest presenting complaints in the history in our patients were fever, generalized body weakness and loss of appetite and most common physical exam findings being pallor, splenomegaly and hepatomegaly. The main presenting complaint of pancytopenia in other studies were anemia, generalized body weakness, shortness of breath, fever, splenomegaly, hepatomegally, bleeding tendencies and edema.[7,14,15] The predominance of fever as a the chief presenting complaint in most of our patients might be due to the higher prevalence of hypersplenism and visceral leishmaniasis in our study, both of which might present with fever. The most common presentations in children were fever and generalized weakness similar to other studies which showed fever and inadequate dietary intake to be the commonest presentations in pediatric age groups.[16]

Hematological Features

The mean hemoglobin level was 8.1 g/dL with almost half of patients (44%) in the range of 8 to 10 g/dL, which is mild anemia according to WHO classificationof anemias.[17] This is different from other studies which show half of their pancytopenic patients to have hemoglobin level below 6g/dl.[13] A study have also shown only three percent of patients having anemia in the mild range. Unlike some studies which showed majority of their pancytopenic population presenting on peripheral morphology with dimorphic anemia 60% and normochromic anemia cases at 15%, our study showed most cases to have normocytic normochromic anemia in peripheral morphology (62.6%).[11] Therefore, our pancytopenic patients, compared to other studies, seem to have mild anemia with normochromic peripheral morphology, which might be related to the commonest causes of pancytopenia in our study.

The findings of bone marrow cellularity were different in our patients in comparison with the bulk of the studies. Marrow cellularity in our study was hypercellurar in 89% of cases, hyperplastic erythropoiesis in 88%, which are explained by the majority of cases who are diagnosed with hypersplenism and visceral leishmaniasis. Most other studies elsewhere show the most common bone marrow presentation to be hypoplastic marrow followed by hyperplastic erythropoiesis in consistency with the common causes in their study which were aplastic anemia and megaloblastic anemia.[18] The most plausible explanation for this variation lies in the difference in the most common etiologies ofpancytopenia.

Causes of Pancytopenia

The study showed the most common cause of pancytopenia in adults to be hypersplenism (45%), visceral leishmaniasis (22%), megaloblastic anemia (20%) and aplastic anemia and acute myeloid leukemia (10%). Studies done in India showed the leading causes of pancytopenia to be megaloblastic anemia and aplastic anemia.[10,12] Pakistani studies, in turn, showed the three leading causes to be aplastic anemia followed by megaloblastic anemia and hypersplenism.[7,13] A study conducted in China also showed the major causes of pancytopenia to be megaloblastic anemia followed by aplastic anemia and myelodysplatic syndromes (MDS).[14] In contrast to the bulk of the literature, our study is consistent with the few studies that show hypersplenism or other infectious causes as the commonest etiologies. A summary presented below shows the major causes of pancytopenia by country and year of publication. (Table 7).

Table 7: Most common causes of pancytopenia in the literature.

Study	Country	Year	Number of cases	Most common cause	Second most common cause
International agranulocytosis and aplastic anemia group.[15]	Israel and Europe	1987	319	Hypoplastic anemia	Myelo-Dysplastic syndrome
Hossain et al.[19]	Bangladesh	1992	50	Hypoplastic anemia	malaria and Kala-azar
Kumar et al.[20]	India	1999	166	Hypoplastic anemia	Megaloblastic anemia
Savage et al.[21]	Zimbabwe	1999	134	Megaloblastic anemia	Aplastic anemia
Khunger et al.[22]	India	2002	200	Megaloblastic anemia	Aplastic anemia
Bajrachyrya et al.[23]	Nepal	2005	10	Hypoplastic anemia	Megaloblastic anemia
Jha et al.[24]	Nepal	2007	148	Hypoplastic anemia	Megaloblastic anemia
Hamid et al.[25]	Yemen	2008	75	Hypersplenism	Malaria
Jain et al.[26]	India	2014	250	Hypersplenism	Malaria
Barik et al.[10]	India	2014	100	Megaloblastic anemia	Aplastic anemia
Gupta et al.[11]	India	2015	50	Megaloblastic anemia	Aplastic anemia
Arshad et al.[17]	Pakistan	2016	330	Megaloblastic anemia	Aplastic anemia
Current Study	Eritrea	2017	75	Hypersplenism	Visceral Leishmaniasis

The causes of pancytopenia in our pediatric population as diagnosed in bone marrow aspiration were visceral leishmaniasis (42%), hypersplenism (38%), acute lymphoblastic leukemia (12%) and aplastic anemia (8%). Other studies show the major causes in children (<18 years of age) to be aplastic anemia and infections/septicemia.[13] A Pediatric age group (1 month to 16 years) study in Pakistan in 2011 also shows the

major causes of pancytopenia to be acute leukemia, aplastic anemia and megaloblastic anemia.[2] An additional cross sectional study enrolling pediatric patients between ages of 2 months to 12 years in Pakistan showed the leading causes of bicytopenia and pancytopenia to be megaloblastic anemia, followed by infective etiology, then aplastic anemia and acute leukemia. The study also showed greater than 70% of patients to be malnourished which explains megaloblastic anemia becoming the leading cause of bicytopenia and pancytopenia in their population.[16] The major causes of pancytopenia in our children were related to tropical infections unlike the other studies.

The major strengths of our study include being the first study on the subject to the best of our knowledge in the Eritrean setting, including all age groups and the fact that it is conducted in the only center in the country were bone marrow examination services can be offered. Despite the above-mentioned strengths, our study had several inherent limitations. The outcomes of patients were not studied as this was a crossectional study and because of lack of hematologic assay for vitamin B12 and folate these 2 entities were not differentiated as both present with megaloblastic anemia. The diagnosis of hypersplenism in our study was not narrowed down to specific causes other than visceral leishmaniasis, which is put as a separate cause. Hypersplenism, however, also includes other infectious causes such as tropical splenomegaly syndrome as sequala of malaria, hematological causes, congestive splenomegaly such as portal hypertension and shistosomiasis and infiltrative causes.[27,28] Therefore, further study is required to establish the specific diagnosis in cases of hypersplenism.

The entry point to the recruitment of subjects to our study was pancytopenic patients who underwent bone marrow examination. This can lead to missing several patients who had been started on treatment without bone marrow aspiration based on peripheral morphology and clinical manifestation alone.

CONCLUSION AND RECOMMENDATION

Our study shows the most common diagnoses in pancytopenic patients to be hypersplenism and visceral leishmaniasis. This can lead to the assumption that in the Eritrean context the most common causes tend to be related more to infectious etiologies rather than nutritional anemias unlike in South East Asian studies. Hence, a larger prospective study is highly recommended in the future to better delineate the etiologies of pancytopenia in our setting. Clinicians are advised to consider tropical infections as important causes for pancytopenia in tropical countries such as Eritrea. In addition, full work up of hypersplenism for specific diagnosis is recommended.

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