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High Prevalence of Morphological Abnormality on Peripheral Blood Cells Among Patients in Public Hospitals, Southern Ethiopia

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Abstract

Introduction: Morphologically abnormal blood cells in peripheral blood of a person reflect underlying pathological condition affecting formation, function, and lifespan of these cells. A properly identified morphological defect in peripheral blood cells is important to manage anemia, leukemia and other disorders of blood. This study aimed to assess magnitude and severity of morphological abnormality in blood cells of patients with abnormal complete blood count in public hospitals found in southern Ethiopia.

Method: A facility-based cross-secional study was conducted from January 01 to March 31, 2019 among five public hospitals in Southern Ethiopia. Peripheral blood sample and socio-demographic data were collected from 423 patients with abnormal complete blood count. Thin blood smear was prepared by Wedge method, stained with Wright's Stain, and examined under microscope by 1000X magnification to detect and characterize abnormality in blood cells' morphology. Descriptive statistical analysis was done using Statistical Package for Social Sciences version 20.0, and results are presented in tables and figures.

Result: Prevalence of blood cell morphological abnormality was 63.8%. From this, 21.8% is marked and 78.2% is moderate abnormality. In 41.9% of the affected patients, the defect involved at least two blood cell types mainly affecting red blood cells. Females (73.8%), children (70.1%) and elderly (82.1%) carried higher prevalence of the abnormality.

Conclusion: High prevalence of abnormality in PBS morphology was observed, chiefly among female, children and elderly. Stakeholders should work to alleviate the high prevalence, with particular attention to women, children and old-age people.

Keywords: Peripheral Blood Smear, Morphological Abnormality, Prevalence, Southern Ethiopia

List of Abbreviations

CBC: Complete Blood Count
ISLH: International Society for Laboratory Hematology
PBS: Peripheral Blood Smear

Introduction

Abnormality in blood cell morphology is a condition whereby an appearance of blood cells vary from the normal. It comprises anomaly in shape, size, color, and internal contents of blood cells, namely RBCs, WBCs and platelets. The presence of abnormal blood cells in peripheral blood of a person indicates underlying pathological condition that affects formation, function, and lifespan of these cells. Genetic, nutritional, infection, chemical and physical factors cause deformity in blood cell morphology. Detection and identification of abnormal blood cell help diagnose blood disorders, select and monitor therapy, and screen pathological conditions in which blood count may remain normal [1,2].

Examination of PBS is an integral part of Hematology laboratory to diagnose and characterize anemia, leukemia, and other disorders of blood. The quantitative derangement in complete blood count (CBC) results and/or display of flags on automated CBC analyzers may trigger the need for PBS analysis [3]. To obtain relevant information from PBS examination, the smear should be well prepared, stained, and examined. Reporting findings from PBS morphological analysis needs, a consensus criteria set by individual laboratory and/or other concerned bodies such as International Council for Standardization in Hematology [4,5]. Properly reported PBS examination joined with CBC data helps clinician to know pathological condition of patient and make evidence-based decision [2,3]. In a pathological condition, morphological defect of a blood cell stems from a various cause. These include deranged hemopoiesis, damage after leaving bone marrow, and amplified production to balance a loss. These states often determine the appearance of abnormal blood cells in peripheral circulation [2,6].

Abnormal findings in RBC morphology include anisocytosis, poikilocytosis, dimorphism and signs of immaturity such as polychromasia and erythroblastemia. Specific findings such as microcytosis, spherocytosis, elliptocytosis, presence of inclusion bodies, fragmented and hypochromic cells represent abnormality of RBC morphology. Damage to an RBC can be due to intrinsic or extrinsic causes. Intrinsic causes include defects on hemoglobin, RBC membrane, and an enzyme. Extrinsic causes cover drugs, chemicals, toxins, heat, infection and mechanical forces. These qualitative defects render the RBC, despite adequate number, unable to fulfil its normal function thereby threatening wellbeing of the patient [2,3].

Abnormality in WBC morphology includes variation in size, in segmentation of the nucleus, in granulation and presence of vacuoles. Segmentation of the nucleus of polymorphonuclear cell, particularly neutrophil is a normal event in its process of maturation from myelocyte stage onwards. The presence of hypersegmented neutrophils, with six or more segments, can be due to megaloblastic anemia, uremia and after cytotoxic treatment. On the other hand, hyposegmented neutrophils, can be due to infection and inherited conditions such as Pelger-Hue¨t anomaly [2,7,8]. Toxic granulation represents an increase in staining density and/or the number of granules. It is commonly seen in bacterial infection, aplastic anemia and myelofibrosis. On the contrary, hypogranular and agranular neutrophils often occur in myelodysplastic syndromes and myeloid leukemia [2,8].

Platelet clumping and giant platelets make-up the major abnormality in platelet morphology. Giant platelets appear in blood during hyposplenism and intensified thrombopoietic conditions such as severe immune thrombocytopenia. Thrombocytosis accompanied with platelet anisocytosis characterizes myeloproliferative disorder. Infections and drugs can result in platelet clumping [1,2,8].

Worldwide prevalence of abnormality in blood cell morphology is growing owing to its multifactorial nature. In a study conducted in Miami, The USA, prevalence of abnormal RBCs was 96% among individuals with sickle cell trait [9]. In Germany, 84%, 98%, and 98% of COVID-19 patients have morphological abnormality in RBCs, WBC and platelet, respectively [10]. In South Africa, the prevalence among neonates was 54.4% [11]. A high prevalence of morphological abnormality with suggestive feature of leukemia, hemolytic anemia and malaria among 0.34%, 6.5% and 4.7% of patients, respectively was reported from Malawi [7]. A study by Kassahun *et al.* 2020, reported 9.3% leukemia in southwest Ethiopia, which denotes the growing burden of hematological disorder in the country [12].

Burden of PBS morphological abnormality is a proxy-indicator of many underlying diseases and hematological disorders such as leukemia and anemia. They worsen burden in various ways, including death, impaired cognitive ability, disability, and raised healthcare cost [13].

Neglecting PBS morphological examination negatively affects management of hematological disorders. According to Beckman et al. 2020, potentially added clinical value would have been missed in 23% of 515 patients, if this test was not done [14]. A misclassified anemia due to neglect PBS examination implies the risk of prolonging avertable patient suffering. Ignoring PBS examination exacerbates the growing burden hematological disorder particularly in developing world, where automation is scarce [15].

Comprehensive evidence obtained from PBS examination fine-tunes clinical decision thereby improving patient outcome. Understanding the prevalence of abnormality in blood cell morphology is crucial to control hematological problem in the respective community. Hence, this study aimed to assess magnitude and severity of this problem in the study area.

Method And Materials

Study Design, Setting and Population

A facility-based cross-sectional study was conducted in five public hospitals from January 01 to March 31, 2019. A total of 423 patients with abnormal CBC results and meeting the inclusion criteria were selected by systematic random sampling from those who came during the study period. We have selected five hospitals, namely Arba Minch General Hospital, Sawula General Hospital, Chencha District Hospital, Karat District Hospital, and Jinka General Hospital based on availability of PBS examination in the last one year [16].

The source population was all clients meeting CBC criteria for PBS examination in public hospitals of the selected zones. The inclusion criteria were increased and/or decreased count of RBC or WBC or platelet compared to the respective reference range, and flagged results. The study population was all selected and consented clients, who came to the public hospitals during the study period.

Sample Size and Sampling Technique

The required sample size for the current study was determined by using single population proportion formula at a confidence level of 95% and 5% margin of error. Due to lack of similar studies, we assumed 50% prevalence of blood cell morphological abnormality and 10% non-response rate, to have the total sample size of 423. This sample size was uniformly distributed to the five hospitals. Patients were selected following a systematic random sampling technique until the required sample size was reached for each hospital [17].

Measurement and Data Collection

Trained data collectors gathered data from patients by using pre-tested, interviewer-administered questionnaires. Hematologist examined Wright's stained PBS following standard operating procedure [2]. A thin smear of peripheral blood was prepared on a slide by Wedge method and air-dried for 30 minutes. The air-dried thin smear was flooded with undiluted Wright's Stain solution for two minutes. Then an equal volume of pH 6.8-buffered water was added and mixed with Wright's stain by gentle blowing. After four minutes of staining, the smear was washed by distil water, and air-dried.

To identify the good working area, the well-dried smear was examined by microscope under 10 X and 40 X objectives. By adding a drop of oil, detail microscopic examination of blood cell morphology was done under 100 X objective oil immersion field (OIF). The size, shape, color of blood cells, and presence of inclusion bodies and immature cells was assessed to determine abnormality of the blood cells. Furthermore, nuclear and cytoplasmic characteristics of WBCs were assessed. After examining 200 OIF, smears with

moderate and/or marked morphological abnormality in any blood cells is declared positive for abnormality. A smear-containing microorganism is declared positive as well.

Quality of the data was assured by pre-testing the questionnaire, training data collectors, and strictly following SOPs and guidelines of manufactures for laboratory procedures.

Data Processing and Analysis

Data were coded, cleaned, and entered into EpiData version 3.1, and then exported to SPSS version 20 (SPSS Inc. Chicago, IL, USA) for analysis. Descriptive analyzes were done to summarize the data. Analysis results were shown using tables and charts.

Operational Definitions

Abnormal CBC Result: An increased or decreased and/or flagged CBC result based on reference range.

Blood Cell Morphological Abnormality: Any morphological defect in any of the three blood cell types that can be graded as moderate and/or marked based on ISLH criteria.

Awareness About Hematological Disorders: A client who has ever heard about any of the common blood disorders (anemia, leukemia and epistaxis).

Result

Background Characteristics of Patients

Mean age of participants was 29.9 years (SD= 18.2), and above half of them are male. Mean income of participants was 1888 ETB, whereas 63 (15%) do not have any monthly income. Two hundred thirteen (48%) of them are aware of hematological disorders (Table 1).

Characteristics	Category	Frequency (%)
Gender	Male	228 (53.9)
	Female	195 (46.1)
Age	< 18 years	108 (25.5)
	18 - 64 years	288 (68.1)
	≥ 65 years	27 (6.4)
Educational status	Illiterate	166 (39.2)
	Literate	257 (60.8)
Monthly income	Yes	196 (46.3)
	No	227 (53.7)
Awareness about blood disorders	Yes	199 (47.0)
	No	224 (53.0)
Willing to use PBS, if requested	Yes	305 (72.8)
	No	118 (27.2)

Table 1: Background characteristics of patients, Southern Ethiopia, 2019

Quantitative CBC Result

The mean RBC, WBC and platelet count was 3.4 X 10^6/μL (SD= 1.9), 16.4 X 10^3/μL (SD= 26.1) and 285.1 X 10^3/μL (SD= 264.1), respectively. RBC count and/or hemoglobin concentration was determined for all patients, but platelet and WBC count was done for 246 (58%) patients only (Table 2).

Characteristics	Category	Frequency (%)
RBCs Count	Decreased	315 (74.5)
	Normal	76 (18.0)
	Increased	32 (7.6)
WBCs Count	Decreased	62 (25.2)
	Normal	78 (31.7)
	Increased	106 (43.7)
Platelets Count	Decreased	95 (38.6)
	Normal	84 (34.1)
	Increased	67 (27.2)

Table 2: Quantitative CBC result of patients, Southern Ethiopia, 2019

Prevalence of Blood Cells Morphological Abnormality

From 3495 CBC samples received during the study period, 1980 (56.6%) have met inclusion criteria for PBS examination. We have included 423 (21.3%) eligible samples in the current study **(Table 3).** Two hundred-seventy (63.8%) samples were positive, having moderate and marked, for PBS morphological abnormality. Three hundred seventy-four (88.4%) of the total eligible patients were denied deserved PBS examination service. To show the missed opportunity, we have done PBS examination for the remaining 374 (88.4%) eligible patients, and we did the overall statistical analysis from total sample size of 423. Prevalence of blood cell morphological abnormality was 63.8% (n= 270), from which 21.8% (n= 59) is marked abnormality (Figure 1).

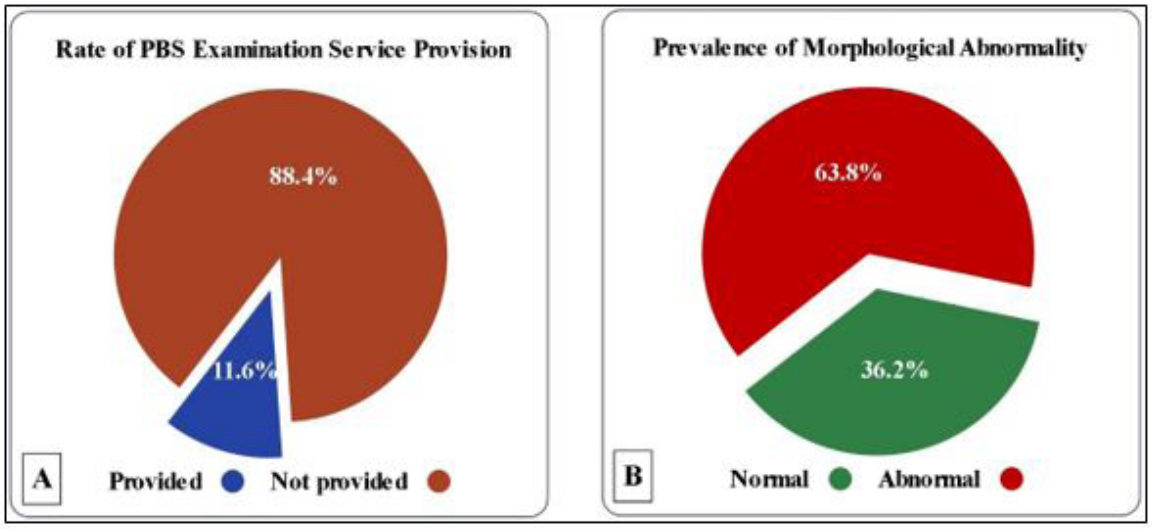

Figure 1: Rate of PBS Examination Service Provision (A) and Prevalence of PBS Morphological Abnormality (B) among Patients, Southern Ethiopia, 2019

From the total 270 patients with morphological abnormality, 192 (71.12%), 144 (53.34%) and 58 (21.48%) have RBCs, WBCs and platelets abnormalities, respectively. On other hand, from those 270 patients with morphological abnormality on their blood cells, in 89 (32.96%), 50 (18.51%), and 18 (6.67%) patients the abnormality involved only RBC, WBC, and platelet, respectively. Whereas, in 73 (27.04%), 19 (7.04%), 10 (3.70%) the abnormality involved RBC and WBC, RBC and platelet, and WBC and platelet, respectively. However, in 11 (4.07%) of the patients, the morphological abnormality affected all the three blood cell types (Figure 2).

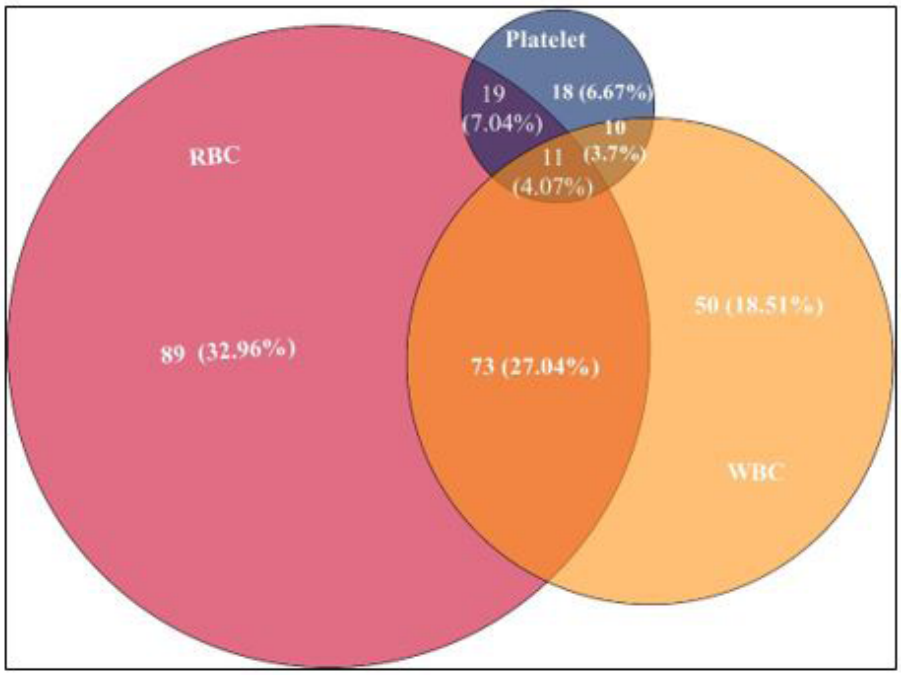

Figure 2: Distribution of Morphological Abnormality by Blood Cell Type in Patients, Southern Ethiopia, 2019

Distribution Morphological Abnormality by Patient Characteristics

The prevalence of blood cells morphological abnormality among females and children was 73.9% and 70.4%, respectively. Slightly higher prevalence of morphological defect was found among patients unable to read and write (77.7%) and those unaware of hematological disorder (63.4%) (Figure 3).

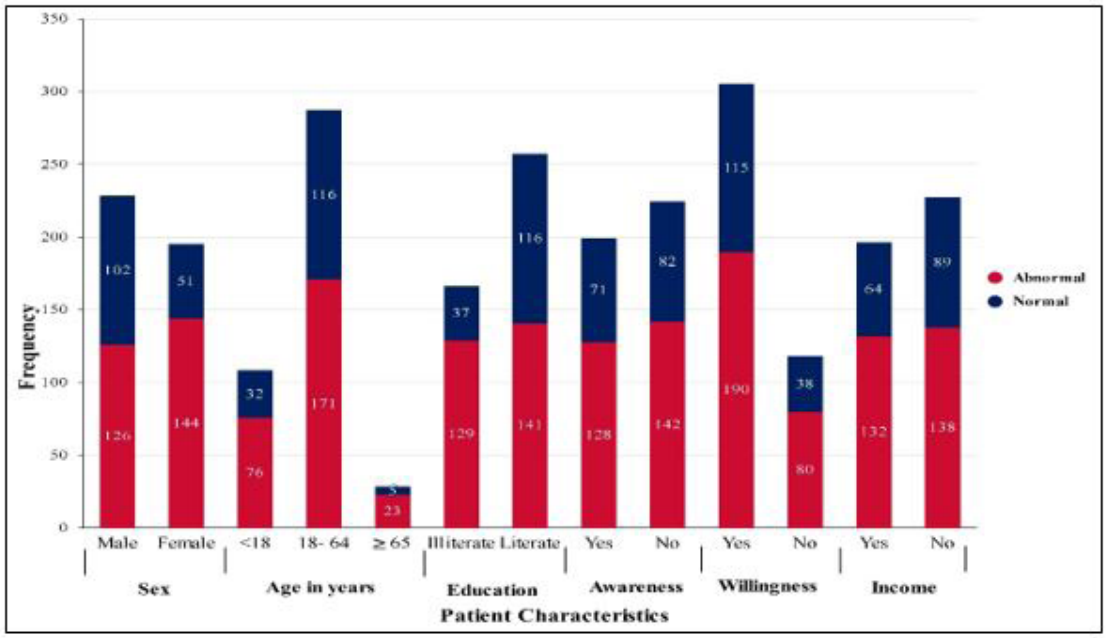

Figure 3: Distribution of Morphological Abnormality on Blood Cells by patient Characteristics, Southern Ethiopia, 2019

Types Of Abnormality on The Morphology of Blood Cells

From 192 patients with RBC morphological defect, 24.1%, 20.5%, and 18.4% of them have variation in size, shape, and color of their RBCs, respectively. Microcytosis, teardrop, and hypochromia were the common abnormalities in RBC morphology. Malaria was the major inclusion body seen in the RBC abnormalities.

From 144 patients with WBC abnormality, vacuolated and hypersegmented neutrophils were seen among 6% of patients. Blast stage of WBCs was found among 1.9% of the participated patients. Platelet clumping was observed among 41 of the patients, taking 70.6% from the total platelet abnormality. Giant platelets and platelets satelitosis were seen among 20 and three patients, respectively (Table 3).

Blood Cell Type	Characteristics	Category	Frequency (%)		
			Moderate	Marked	Total
RBC	Size	Microcytic	73 (84.8)	13 (15.2)	86
		Macrocytic	14 (77.8)	4 (22.2)	18
	Shape	Echinocyte	4 (57.1)	3 (42.9)	7
		Acantocyte	2 (66.7)	1 (33.3)	3
		Sickle Cell	3 (100)	0 (0)	3
		Tear drop	19 (86.3)	3 (15.7)	22
		Target	18 (81.8)	4 (18.2)	22
		Ovalocytes	16 (80.0)	4 (20.0)	20
		Schistocytes	7 (70.0)	3 (30.0)	10
		Stomatocyte	5 (83.4)	1 (16.6)	6
	Color	Polychromic	34 (69.4)	15 (30.6)	49
		Hypochromic	63 (79.7)	16 (20.3)	79
	Inclusion bodies	Basophilic stippling	NA	NA	3 (100)
		Heinz Bodies	NA	NA	3 (100)
		Howell-Jolly Bodies	NA	NA	5(100)
		Malaria	NA	NA	7 (100)
	Rouleaux formation	Yes	NA	NA	15 (100)
	Immature RBCs	Reticulocytes	NA	NA	49 (100)
		Nucleated RBCs	NA	NA	31 (100)
		RBC blast	NA	NA	6 (100)
WBC	Segmentation	Hyposegmented	11 (68.7)	5 (31.3)	16
		Hypersegmented	9 (81.8)	2 (18.2)	11
	Granulation	Hypogranular	6 (100)	0 (0)	6
		Hypergranular	3 (42.8)	4 (57.2)	7
		Toxic granulation	8 (66.7)	4 (33.3)	12
	Vacuolation	Yes	15 (65.2)	8 (34.8)	23
	Immature stages of WBCs	Other immature WBC stages	NA	NA	23 (100)
		WBC blast	NA	NA	8 (100)
Platelets	Giant Platelets	Yes	16 (80.0)	4 (20.0)	20
	Platelet Clumping	Yes	36 (87.8)	5 (12.2)	41
	Platelet satelitosis	Yes	2 (66.7)	1 (33.3)	3

Table 3: Types of morphological abnormality among Patients, Southern Ethiopia, 2019

Severity of Blood Cells Morphological Abnormality

From the 270 patients with blood cell morphological defect, 59 (21.8%) and 211 (78.2%) have marked and moderate defect, respectively. Prevalence of severe abnormality in blood cells morphology among females, and those lack monthly income was 25.0% and 23.2%, respectively (Table 4).

Characteristic	Category	Severity		Total
		Moderate (%)	Marked (%)	
Gender	Male	103 (81.7)	23 (18.3)	126
	Female	108 (75.0)	36 (25.0)	144
Age	< 18 years	60 (78.9)	16 (21.1)	76
	18- 64 years	130 (76.0)	41 (24.0)	171
	≥ 65 years	21 (91.3)	2 (8.7)	23
Education	Illiterate	103 (79.8)	26 (20.2)	129
	Literate	108 (76.6)	33 (23.4)	141
Awareness	Yes	95 (74.2)	33 (25.8)	128
	No	116 (81.7)	26 (18.3)	142
Willingness	Yes	143 (75.2)	47 (24.8)	190
	No	68 (85.0)	12 (15.0)	80
Income	Yes	105 (79.5)	27 (20.5)	132
	No	106 (76.8)	32 (23.2)	138

Table 4: Severity of morphological abnormality by patient characteristics, Southern Ethiopia, 2019

Discussion

The overall prevalence of morphological abnormality in blood cells of the patients was 63.8%. Nearly two-third of the patients carried defect in the morphology of their blood cells. This indicates significant proportion of patients have qualitatively abnormal blood cells that cannot function properly. These cells are impaired to deliver nutrients and oxygen, fight infection, and stop bleeding thereby put the patient in difficulty to support life [1]. Our finding is greater than the result from the study conducted among inpatients at Chris Hani Baragwanath Academic Hospital, South Africa, where 54.4% prevalence was seen. This inconsistency could be due to the inclusion of suspected patients with deranged CBC in our study than the study in South Africa that focused on neonates [11].

The prevalence of morphological abnormality by RBCs is 45.39% (n= 192), contributing for 71.12% of the overall prevalence. The main morphological abnormalities in RBCs were variation in size, shape, and color. Microcytosis, hypochromia, and teardrop cells. Malaria was the predominant inclusion body found in the RBCs. Our findings agreed with study findings from India, where a higher proportion of microcytosis (53.08%), dimorphism (46%), and presence of normoblasts (16.8%) has been reported [18]. The higher prevalence of microcytic-hypochromic cells together with high poikilocytosis suggests microcytic-hypochromic anemia, such as iron deficiency anemia. This might have emanated from the hidden micronutrient deficiency among the patients. Increased numbers of nucleated cells and polychromasia can be due to anemia and *P. falciparum* infection that can trigger compensatory response secondary to hemolysis [1,2].

The prevalence of morphological abnormality by WBCs is 34.04% (n= 144), taking 53.34% of the overall prevalence. Abnormal granulation was observed among 5% of patients with WBCs abnormality. This result is lower than the report from a study conducted in India, where 20.4% neutrophil leukocytosis with toxic granules was observed [18]. This discrepancy might be secondary to the suggested infectious disease and inflammation causes for the toxic granulation in that study. Hypogranular WBCs were detected

among 5% of the patients. Blast stages of WBCs were observed among 6% of the patients. These immature cells raise the suspicion for malignancy in WBCs. This finding is consistent with a finding from Malawi, where the left shift was reported among 16% of WBCs [7,18,19].

The prevalence of platelet morphological defect was 13.7% (n= 58), comprising 21.5% of the overall prevalence. Patients with qualitative defect in their platelets are at increased risk to suffer from defect in hemostasis [1]. Our finding is higher than a result from India that reported 11.5% thrombocyte defect among patients. The difference in population and study area might have influenced the observed variation. The suggested causes of this defect is drug or infection such as malaria that could have also lowered the number of RBCs and WBCs [18,19].

From the 270 patients with blood cell morphological defect, 21.8% (n= 59) and 78.2% (n= 211) have severe and moderate defect, respectively. Severe defect is more common, 21.8%, among patents with RBC morphological defect. The prevalence of morphological abnormality was higher among females, illiterate, children, and those with lower monthly income compared to their respective counterparts. This result is similar to the result of study done in India [18]. This can partly be linked to the variation of hematological parameters by gender and age. Besides, these population segments have increased susceptibility to different infectious diseases that can alter the normal hematological cells [1,2].

A raised disorder in morphology of RBCs, particularly elevated polychromasia, and nucleated RBCs was observed. Furthermore, few patients' blood picture showed malaria with schistocytosis signaling hemolytic anemia comparable to the report by Latham et al. [3,7]. Considerable proportion of patients carried microcytic-hypochromic blood picture accompanied with marked poikilocytosis (dominated by target cells and teardrop cells) indicative of microcytic-hypochromic anemia, particularly iron deficiency anemia. The domination of such microcytic-hypochromic cells was observed among anemic pregnant women in refugee camps of Gambella [20]. Besides, oval macrocytosis, including the oval macrocytes, hypersegmented neutrophils and Howell Jolly bodies were coincided among few patients. According to reports from Benin and India, such findings suggest for nutritional deficiency among the patients [18,21].

Above two per cent of patients' blood cells exhibited toxic granulation and vacuolation in their WBCs accompanied with anisocytosis (dominated by microcytic-hypochromic cells) and acantocyte. This might be secondary to infection in organs involved in hematopoietic process and/or drug toxicity. Similar results were reported from Malawi and Turkey [7,22].

The proportion of myeloblasts and other immature stages of WBCs was found in more than five percent of the patients. In few cases this finding concurred with hypogranular WBCs, anemia and immature series in RBCs lineage, suggesting for acute leukemia. Similar findings were reported from studies in Benin, Malawi and India [7,18,21]. Patients with hyposegmented-hypogranular polymorphonuclear cells accompanied with spectrum of immature cells and giant platelets were observed. This suggests for myelodysplastic syndrome, and similar findings have been reported from Malawi [1,7,9,23].

Generally, considerable amount of missed opportunity is apparent in the face of the high prevalence of blood cell morphological abnormality mainly among children and women. Most importantly, PBS examination remains part and parcel of clinical laboratory service characteristically cost-effective and least invasive source of information for clinical decision-making.

Strength and Limitation of the Study

We have showed the burden and missed opportunity due to neglecting this low-cost and high-yield laboratory service. However, this study did not incorporate further hematological tests to explicitly show the detailed characteristics of the hematological problem.

Conclusion and Recommendation

The prevalence of blood cell morphological abnormality is high. Women, children and elderly carried higher prevalence implying substantial burden of hematological disorder in the area. Nevertheless, few patients received PBS examination service. This indicates negligence to the role of this cost-effective and valuable test.

We strongly recommend stakeholders to alleviate the high prevalence of blood cell morphological abnormality among women and children. The hospitals should initiate and strengthen PBS examination service. Besides, health professionals should utilize this test to address this prominent hematological problem in the area.

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