



Hematological Abnormalities and Associated Factors Among Undernourished Under-Five Children Attending University of Gondar Specialized Referral Hospital, Northwest Ethiopia

This article was published in the following Dove Press journal:
Journal of Blood Medicine

Solomon Getawa
Zegeye Getaneh 
Mulugeta Melku 

Department of Hematology and
Immunohematology, School of
Biomedical and Laboratory Science,
College of Medicine and Health Science,
University of Gondar, Gondar, Ethiopia

Introduction: The hematopoietic system is one of the systems which can be affected by malnutrition, leading to impaired production of all blood cell lines. Undernourished children with hematological abnormalities like anemia are at higher risk of mortality. Therefore, this study aimed at determining the magnitude and associated factors of hematological abnormalities among undernourished under-five children attending at the University of Gondar Specialized Referral Hospital, Northwest Ethiopia.

Methods and Materials: An institution-based cross-sectional study was conducted on a total of 251 undernourished under-five children at University of Gondar Specialized Referral Hospital from January to May 2020. A convenient sampling technique was employed to select study participants. Data were collected using a pretested structured questionnaire. Blood samples were collected for complete blood count which were determined by Sysmex KX-21N analyzer. Stool sample was processed via direct wet mount. Thin and thick blood films were examined to assess malaria parasite. The data were entered to EpiData version 4.6.0.0 and analyzed using SPSS version 23 software. Bi-variable and multi-variable binary logistic regression model were fitted to identify factors associated with hematological abnormalities. A p-value <0.05 in the multivariable analysis was considered as statistically significant.

Results: The overall magnitude of anemia, leukocytosis, thrombocytosis, thrombocytopenia, and leukopenia was 53.4%, 26.7%, 23.9%, 8%, and 2.8%, respectively. Being male, age 6–23 months, high birth order, intestinal parasite infection, edema, not eating vegetables and fruits, and paternal occupation were found to be associated with anemia. Only the age of a child was associated with leukocytosis in undernourished children.

Conclusion: The current study demonstrated the predominant existence of anemia, leukocytosis, and thrombocytosis among undernourished under-five children. Therefore, early diagnosis, monitoring and setting intervention strategies for anemia especially among children under two years old are required to prevent further complication.

Keywords: anemia, leukocytosis, thrombocytosis, leukopenia, thrombocytopenia, children, undernutrition, Ethiopia

Correspondence: Solomon Getawa
Department of Hematology and
Immunohematology, School of Biomedical
and Laboratory Science, College of
Medicine and Health Science, University
of Gondar, Gondar, Ethiopia
Tel +251-914-665-736
Email solomon2525geta@gmail.com

Introduction

Protein-energy malnutrition (PEM) is a pathological conditions resulted from lower ingestion of various proportions of protein, calories, and micronutrients.¹ It is a major health concern particularly in developing countries, mainly in under-five children.^{2,3} Globally in 2019, 144 million (21.3%) and 47 million (6.9%) under-five

children suffer from stunting and wasting, respectively. Of them, 40% and 27% of stunted and wasted children lived in Africa, respectively.⁴ The prevalence of stunting, wasting, and underweight was 37%, 7%, and 21%, respectively, in Ethiopia.⁵ Undernutrition includes underweight (Z score of weight-for-age (WAZ) <-2), stunting (Z score of height-for-age (HAZ) <-2), and wasting (Z score of weight-for-height (WHZ) <-2).⁶ Children suffering from stunting and wasting may not attain their full possible height and weight; and may have shown an impaired cognitive potential, weakened immunity, and developmental delays.⁴

PEM results in widespread alterations in organ and system function.^{1,7} In the hematological system, the changes affect all blood cell lines. This hematological alteration includes anemia, changes in reticulocyte count, leukocytosis, and changes in the hematopoietic microenvironment of the bone marrow (BM) have been documented in previous studies.^{1,3,8,9} In an animal model, PEM produces alterations in hematopoiesis that are caused by impairment of the BM stroma and alterations in the hematopoietic progenitors' cell cycle with a higher number of cells in the G0/G1 phase.¹⁰ PEM alters granulocyte-macrophage colony-stimulating factor and macrophage colony-stimulating factor production by macrophages which leads to diminished immune response and blood cell formation and maturation.¹¹ It also alters lymphohematopoietic organs like BM, spleen, and thymus which leads to anemia, leukopenia, alters the immune system, and increases susceptibility to infections.¹²

Low red blood cell (RBC) count resulting anemia has a common feature of PEM. The need for protein and energy during erythropoiesis by BM justifies the occurrence of anemia in malnutrition.¹³ A decrease in erythropoietin, occurring due to the reduced ingestion of protein and reduced RBC production in adaptation to a smaller lean body mass may also be responsible for anemia.^{14,15} Amazingly, the prevalence of anemia among this population reaches to 97%.¹⁶ Stunted, underweight, and wasted children are more likely to be anemic than well-nourished children.¹⁷ Studies revealed that severely malnourished children with anemia are at higher risk (2.62 times) of mortality compared to non-anemic.^{18,19} It is a leading cause of pediatric morbidity, hospitalization, and mortality. Moreover, anemia affects the cognitive performance and physical growth of the children.²⁰ Anemia in PEM is unlikely to respond to treatment unless the associated infection is brought under control.¹⁵ The cause of anemia in PEM children may be due

to iron and folate deficiency,^{16,21,22} vitamin A deficiency, protein deficiency,²³ hemolysis due to an alteration in the antioxidant mechanisms in erythrocytes, infection, and infestation with parasites.^{24,25}

Leukopenia and leukocytosis that occurs in PEM as a result of an infection by establishing a malnutrition–infection relationship in which the poor nutritional status disrupts leukopoiesis.²⁶ The occurrence of leukocytosis in PEM is usually accompanied by infectious processes or chronic disease.^{9,27} Leukopenia is present in children with PEM if they are not accompanied by other diseases. Leukopenia was observed in children with acute malnutrition in up to 9% of cases.²⁸ It is characterized not only by a decrease in the leukocyte count but also by impaired processes carried out by the leukocytes. Mainly in newborns and small children, PEM provokes thymus atrophy that leads to leukopenia, decreases CD4/CD8 ratio, increases number of immature T cells in the periphery, and impaired phagocytosis by macrophages.²⁹ This in turn may cause immune suppression and increase susceptibility to infection. This may put a child at greater risk of dying from such infections, increase hospitalization dates, and contribute to delayed recovery.¹

In children with malnutrition, a decreased platelet count may be attributed to a decrease in BM activities which indirectly affect megakaryocyte functions.^{30,31} This may also be due to platelet activation with an infection like malaria which shortened the life span of platelet during platelet pathogen interaction and pathogens can induce removal of platelets from the circulation by triggering their clearance through phagocytosis.³² Thrombocytosis is another hematological alteration in undernourished children that could be associated with infection.³³ In Ethiopia, undernutrition is a major public health problem and a preliminary diagnosis in 20% of pediatric hospital admissions.³⁴ The fatal effect of the disease in relation to hematological features is one concern where attentions have not yet got. Therefore, this study aimed at determining hematological abnormalities and associated factors among undernourished under-five children attending at the University of Gondar Specialized Referral Hospital.

Methods and Materials

Study Design, Period and Area

An institution-based cross-sectional study was conducted at the University of Gondar Specialized Referral Hospital from January to May 2020. The hospital is located in the

central Gondar zone, Gondar town, Amhara Regional State. It is located at 738 km far from the capital city of Ethiopia, Addis Ababa, and 180 km far from the capital city of the region, Bahir Dar. The town is situated at 2133 meters elevation above sea level. Currently, the town has one referral hospital, five government health centers, and more than 45 private clinics. The hospital provides different medical services for more than 7 million people in the zones and peoples of the neighboring zones through different wards and outpatient departments. It has 512 beds, of which 70 beds are allocated to the pediatric ward. This ward has a separate room or center for the treatment of malnourished children.³⁵

Population

All undernourished under-five children who were attending at the University of Gondar Specialized Referral Hospital were taken as the source population whereas, undernourished under-five children who attended at the University of Gondar Specialized Referral Hospital during the study period, and willing to participate in the study were considered as the study population.

Inclusion and Exclusion Criteria

All under-five children diagnosed as undernourished and fulfill criteria for severe acute malnutrition (SAM) treatment (WHZ less than -3 z-score); for moderate acute malnutrition (MAM) treatment (WHZ ≥ -3 to less than -2 z-score), children with z-score below -2 standard deviations for their WAZ and HAZ, and before receiving treatment at the University of Gondar Specialized Referral Hospital were included in the study. But undernourished children who had been receiving iron and vitamin supplements in the last four weeks, children who received a blood transfusion in the last three months, and children who had been confirmed chronic diseases like renal failure, cancer, and liver diseases were excluded. Children with tuberculosis and human immunodeficiency virus were also excluded from the study.

Sample Size Determination and Sampling Technique

The sample size calculation was based on a single population proportion formula, $[n = (Z \alpha/2)^2 p (1-p)/d^2]$. By taking the prevalence of anemia (61%) among undernourished (stunted) children which was conducted in Ethiopia.¹⁷ The total sample size was calculated as

follows: $n = (Z \alpha/2)^2 p (1-p)/d^2 = (1.96)^2 \times 0.61 (1-0.61)/(0.05)^2$ then $n_i = 366$. But, the estimated number of undernourished children attending the hospital is $<10,000$. For such situation, finite population correction formula is recommended and the sample size was adjusted as follows: $n_f = n_i/1+n_i/N = 366/1+366/800 = 251$. Where, d = margin of error between the sample and the population ($d=5\%$), n_i = initial sample size, n_f = final sample size, N = total sample size of the target population, $Z = 95\%$ confident interval, $Z\alpha/2 = 1.96$ and $P=61\%$. A convenience sampling technique was used to select study participants.

Operational Definitions

Anemia: defined based on the altitude adjusted hemoglobin (Hb) values less than 11 g/dl for children <5 years old and its severity is classified as Mild anemia: if Hb is between 10 and 10.9 g/dl, Moderate anemia: if Hb level is between 7 and 9.9 g/dl and Severe anemia: if Hb level of less than 7 g/dl.³⁶ Morphologically based on mean corpuscular volume (MCV), anemia is classified as microcytic (MCV <80 fl), normocytic (MCV between 80 and 100 fl), and macrocytic (MCV >100 fl).³⁷ Thrombocytopenia is defined as platelet count below $150,000/\text{mm}^3$ while thrombocytosis is defined as platelet count above $450,000/\text{mm}^3$. Moreover, leukopenia is defined as a WBC count below $4000/\text{mm}^3$ while, leukocytosis is defined as a WBC count above $12,000/\text{mm}^3$.^{3,38}

Data Collection and Laboratory Methods

Socio-Demographic, Feeding, and Clinical Data

A written informed consent was obtained from the parents. A detailed and thorough history along with complete anthropometry and physical examination was done. Feeding characteristics were collected based on a food frequency questionnaire that was used previously in Ethiopia and modified based on the reviewed literature.³⁹ The frequency variable coded as never, once a month, 2–3 times a month, once a week, 2–3 times a week, and at least once a day. Data on socio-demographic characteristics of children, feeding characteristics, breastfeeding status, complimentary food supplementation status, and characteristics of parents/guardian were collected using structured pre-tested questionnaire via face-to-face-interview of children's parents/guardians. The aforementioned data were collected by trained clinical nurses working in the nutritional rehabilitation center.

Hematological Analysis

Under aseptic conditions, 3 mL venous blood was collected by venipuncture from superficial veins of the antecubital fossa. After the blood specimen collection, then transferred into an ethylene diamine tetraacetate (EDTA) test tube and gently mixed to prevent clotting. The blood specimen was analyzed using Sysmex KX-21N automated hematology analyzer to determine complete blood count.

Parasitological Examination

From each study participant, pea-size (1gm) fresh stool samples were collected following the standard operating procedures (SOPs) in clean and labeled leak-proof stool cups. Stool specimens were processed by the wet mount technique. A small amount of stool sample was put on microscopic slides and a drop of normal saline was added. Then, wooden applicator sticks were used to mix the sample and the saline, and cover glass was applied. Finally, using 10x and 40x microscope objectives helminths eggs, larvae, and cysts of protozoan parasites were assessed. Children who were febrile were screened for malaria parasites. Thick and thin blood smear slides were prepared, stained with Giemsa (10%), and examined microscopically for malaria parasites. Malaria was excluded when thick blood films were reported negative after examining 100 fields under 100x oil immersion objective.

Data Quality Control

To ensure data quality, the questionnaire had been prepared in English and translated to the local language (Amharic) and then re-translated back to English to see its consistency and pre-testing was done to ensure its validity. The performance of the automated hematology analyzer was checked by running three levels of (Normal, Low, and High) controls. Known malaria-positive and negative blood smear were used to prepare quality control (QC) materials for thick and thin films to check the quality and performance of the Giemsa stain, as well as stool examination, was performed after checking the working normal saline solution.

Data Analyses and Interpretation

Data were entered into EpiData version 4.6.0.0 statistical software then exported to Statistical Package for Social Sciences (SPSS) version 23 software for analyses. Descriptive statistics (mean, median, frequency, percentage) were used to summarize the characteristics of study

participants; and the results were presented in tables and charts. Shapiro–Wilk test was done to check the normality of data. A binary logistic regression model was fitted to identify factors associated with hematological abnormalities. The Hosmer-Lemeshow goodness-of-fit test was used to assess the fitness of the model. Independent variables having a p-value less than or equals to 0.2 in bi-variable analyses were included in the multi-variable analyses to control confounders. Both crude odds ratio (COR) and adjusted odds ratio (AOR) with the corresponding 95% confidence interval (CI) were calculated to show the strength of association. P-value <0.05 in the multi-variable binary logistic regression model was considered as statistically significant.

Ethical Approval and Consent to Participate

Ethical approval was obtained from University of Gondar, College of Medicine and Health Sciences, School of Biomedical and Laboratory Sciences, Research and Ethical Review Committee (Reference number SBMLS/2438/12) before data collection. Permission letter to conduct the study were obtained from the University of Gondar Specialized Referral Hospital Chief Executive Officer. Written informed consent was obtained from the child's parents. To ensure confidentiality, study subjects were identified using codes, and only authorized persons accessed the collected data. Study participants who had abnormal results were notified to the physician and nurse who are working at the nutritional center for proper patient care.

Results

Socio-Demographic Characteristics

A total of 251 undernourished under-five children were participated in the study; of the participants, 126 (50.2%) were males. The age of study participants ranged from 6 to 59 months. The median interquartile range (IQR) age of the study participant was 19 months (10–35). Regarding their age distribution, 151 (60.2%) were between 6 and 23 months, and 38 (15.1%) were between 24 and 35 months. Parents/guardians of the participating children were interviewed. Out of 251 respondents, 133 (53%) were urban dwellers and 217 (86.5%) were married. Regarding their educational status, 122 (48.6%) of their mothers and 98 (39%) fathers had no formal education. The majority, 199 (79.2%), of mothers were housewives and 108 (43%) of fathers were farmers (Table 1).

Table 1 Socio-Demographic Characteristics of Undernourished Under-Five Children and Their Parents/Guardians Attending at the University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020

Variable	Category	Frequencies	Percentages
Gender	Male	126	50.2
	Female	125	49.8
Age (months)	6–23	151	60.2
	24–35	38	15.1
	36–47	25	10
	48–59	37	14.7
Birth order	First	87	34.7
	Second	69	27.5
	Third	47	18.7
	Fourth and above	48	19.1
Residence	Rural	118	47
	Urban	133	53
Monthly income of the house (Et. Birr)	≤1000	90	35.9
	1001–2000	68	27.1
	>2000	93	37
Marital status of parents	Married	217	86.5
	Single	15	6
	Divorced	19	7.5
Maternal educational status	No formal education	122	48.6
	Primary education (1–8)	85	33.9
	Secondary education (9–10) & above	44	17.5
Paternal educational status	No formal education	98	39
	Primary education (1–8)	92	36.7
	Secondary education (9–10) and above	61	24.3
Maternal occupational status	House wife	199	79.2
	Government employee	29	11.6
	Daily laborer	14	5.6
	Private	9	3.6
Paternal occupational status	Farmer	108	43
	Government employee	56	22.3
	Daily laborer	37	14.7
	Private	50	20
Family size	≤4	140	55.8
	>4	111	44.2
Number of under-five children in the house	1	161	64.1
	>1	90	35.9

Note: 35.10ETB = 1 \$US.

Abbreviation: ETB, Ethiopian Birr.

Clinical and Feeding Characteristics

Among 251 study participants, 138 (55%) and 141 (56.2%) had diarrhea and fever in the last 2 weeks before data collection, respectively. Edema was present in 14 (5.6%) of children. The majority, 216 (86.1%), of children were exclusively breastfed in the first 6 months of their

life. Forty-three (17.1%) and 6 (2.4%) of the children were infected with intestinal and malaria parasites, respectively. Out of 43 children infected with intestinal parasites, 14 (32.5%) and 8 (18.6%) of children were infected with *Ascaris lumbricoides* and *Hookworm* parasites, respectively (Table 2).

Table 2 Clinical and Feeding Characteristics of Undernourished Under-Five Children Attending at the University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020

Variables	Category	Frequencies	Percentages
Presence of diarrhea	Yes	138	55
	No	113	45
Presence of fever	Yes	141	56.2
	No	110	43.8
Presence of edema	Yes	14	5.6
	No	237	94.4
Exclusive breast feeding	Yes	216	86.1
	No	35	13.9
Introducing complimentary food	Before 6 months	34	13.5
	After 6 months	217	86.5
Meat consumption	Yes	81	32.3
	No	170	67.7
Milk intake	Yes	116	46.2
	No	135	53.8
Vegetable and fruit intake	Yes	116	46.2
	No	135	53.8
Cereal foods consumption	Yes	178	70.9
	No	73	29.1
Malaria	Yes	6	2.4
	No	245	97.6
Intestinal parasite	Yes	43	17.1
	No	208	82.9
Type of intestinal parasite (N=43)	<i>Ascaris lumbricoides</i>	14	32.5
	<i>Hook worm</i>	8	18.6
	<i>Entamoeba histolytica</i>	7	16.3
	<i>Hymenolepis nana</i>	6	14.0
	<i>Giardia lamblia</i>	6	14.0
	<i>Strongyloides stercoralis</i>	2	4.6

Magnitude of Hematological Abnormalities

The altitude adjusted Hb level among undernourished children ranges from 1.9g/dl to 16.4 g/dl, with a median (IQR) value of 10.08 g/dl (9.5–11.8). The overall magnitude of anemia as defined by Hb levels lower than 11 g/dl adjusted for altitude above sea level was found to be 53.4% (95% CI: 47.2–59.6%). Of them, 74 (55.2%) were males and 76 (56.7%) were from rural dwellers. The highest frequency of anemia was among children aged groups 6–23 months (73.1%) while the least was among children age 36 to 47 months (5.2%). The range of WBC count was 2.2 to 25×10^3 cells/ μ L, with a median (IQR) value of 9×10^3 cells/ μ L (6.5–12.6). Leukopenia was detected in 2.8% (95% CI: 0.74–4.84%), whereas leukocytosis was

detected in 26.7% (95% CI: 21.18–32.20%) of the children. The range of platelet count was 27 to 781×10^3 cells/ μ L, with a mean (\pm SD) value of $349.3 \pm 145.03 \times 10^3$ cells/ μ L. Thrombocytopenia was detected in 8% (95% CI: 4.59–11.34%), whereas thrombocytosis was detected in 23.9% (95% CI: 18.59–29.22%) of the children (Table 3 and Figure 1).

Severity and Morphological Classification of Anemia

The severity of anemia was classified based on their Hb levels. Of 134 anemic children, 17.2% were found to be severely anemic, whereas 44% and 38.8% were moderately

Table 3 Hematological Parameters of Undernourished Under-Five Children Attending at the University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020

Parameters	Range	Median (IQR)	Mean \pm SD
WBC ($\times 10^3/\mu\text{L}$)	2.2–25.0	9(6.5–12.6)	–
Hb (g/dl)	1.9–16.4	10.08(9.5–11.8)	–
Hct (%)	11.8–53.9	35.1(31.8–38.3)	–
MCHC(g/dl)	20.3–78.1	32.8(31.6–33.9)	–
Lymphocyte ($\times 10^3/\mu\text{L}$)	0.4–12.1	3.7(2.6–5.2)	–
RBC ($\times 10^3/\mu\text{L}$)	1.22–7.49	–	4.59 \pm 0.81
MCH(pg)	12.0–35.6	–	32.63 \pm 4.83
MCV(fl)	39.0–107.7	–	75.73 \pm 9.54
Platelet ($\times 10^3/\mu\text{L}$)	27–781	–	349.3 \pm 145.03

Abbreviations: WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; IQR, interquartile range; SD, standard deviation.

and mildly anemic, respectively. Morphologically based on their MCV obtained from the complete blood count result, the most common type of anemia was microcytic anemia (73.1%), followed by normocytic anemia (25.4%). Two children (1.5%) had macrocytic anemia (Figure 2).

Anemia and Associated Factors

To determine the association, bi-variable binary logistic regression analyses was done. Based on the analyses, children aged 6–23 months, male in sex, being infected with intestinal parasite, being fourth and above in birth order, fever, having edema, not eating meat, not eating vegetables and fruits, being rural in residence, being children of fathers with no formal education, and being children of fathers who are farmers, and daily laborer was significantly associated with the magnitude of anemia. However, in the multi-variable binary logistic regression analyses model, being male (AOR= 1.99; 95% CI: 1.10–3.61), being aged between 6 and 23 months (AOR= 5.45; 95% CI: 2.13–13.93), being fourth and above in birth order (AOR= 3.01; 95% CI: 1.20–7.54), intestinal parasite infestation (AOR= 2.87; 95% CI: 1.25–6.63), a child with edema (AOR= 5.33; 95% CI: 1.21–23.56), not eating vegetables and fruits (AOR= 2.05; 95% CI: 1.03–4.10) and parental occupation (daily laborer) (AOR= 3.13; 95% CI: 1.14–8.55) have remained associated factors with anemia in undernourished under-five children (Table 4).

Leukocytosis, Thrombocytosis, Thrombocytopenia, and Their Associated Factors

Both bi-variable and multi-variable binary logistic regression analyses were done to assess associated factors for leukocytosis. The variables that were statistically

associated with leukocytosis were only child ages between 36 and 47 months (AOR= 4.05; 95% CI: 1.13–14.55) (Table 5). To assess factors associated with thrombocytopenia and thrombocytosis, both bi-variable and multi-variable binary logistic regression analyses were done. Accordingly, any of the variables did not show statistically significant association in the multi-variable binary logistic regression model.

Discussion

The hematopoietic tissues have a high rate of cell renewal and proliferation that require a sufficient supply of nutrients, and may thus be altered by a deficiency of nutrients.¹ Experimental studies suggested that hematological abnormalities during PEM occur due to alterations of hematopoiesis in the BM, hematopoietic progenitors' cell cycle,¹⁰ lymphohematopoietic organs,¹² and alteration of the production of colony-stimulating factor by macrophages.¹¹

In the current study, anemia was the most prevalent hematological abnormalities in undernourished children (53.4% (95% CI: 47.2–59.6)). This finding was in agreement with previous literature.^{14,16,30} According to WHO, anemia is considered a severe public health problem if the magnitude is $\geq 40\%$.³⁶ Accordingly, the magnitude of anemia in the current study indicates that anemia is a severe public health problem among undernourished under-five children in the study area. Low intake of iron-rich foods and diminished nutrient absorption caused by changes in the gastrointestinal epithelium of undernourished individuals contribute towards the development of anemia.⁴⁰ Besides, an interaction between adaptation to inadequate food intake and the impact of other stresses associated with infection or dietary imbalance may lead to anemia.⁴¹

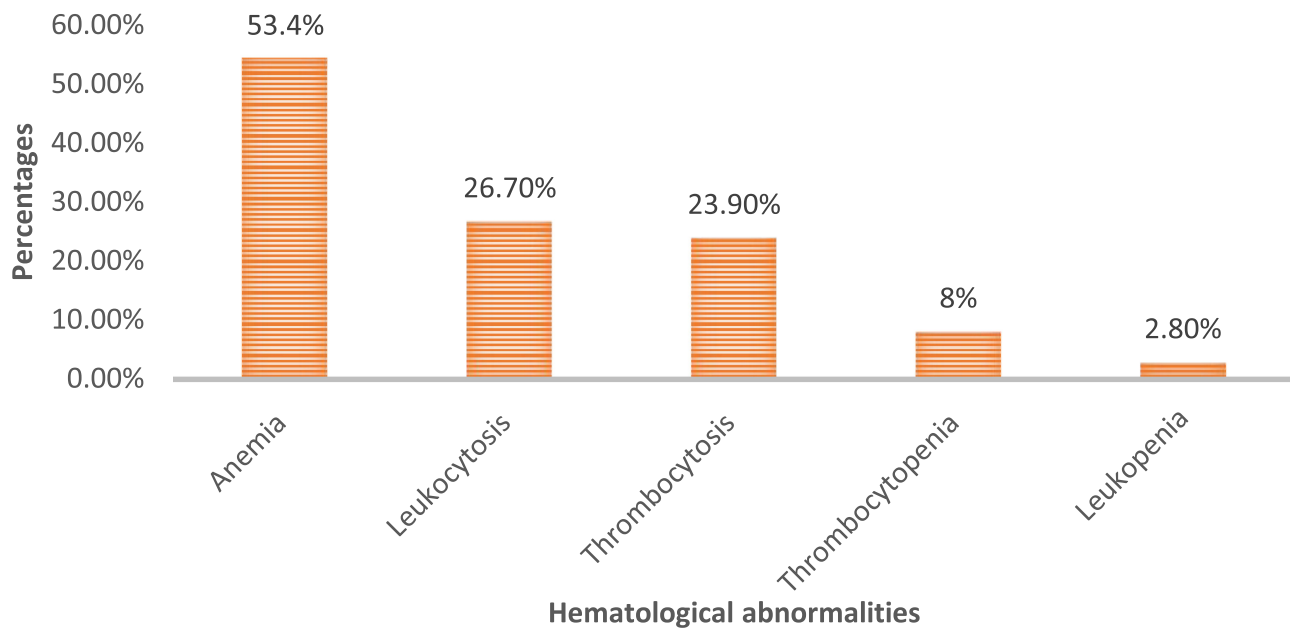


Figure 1 Magnitude of hematological abnormalities among undernourished under-five children, University of Gondar Specialized Referral Hospital, 2020.

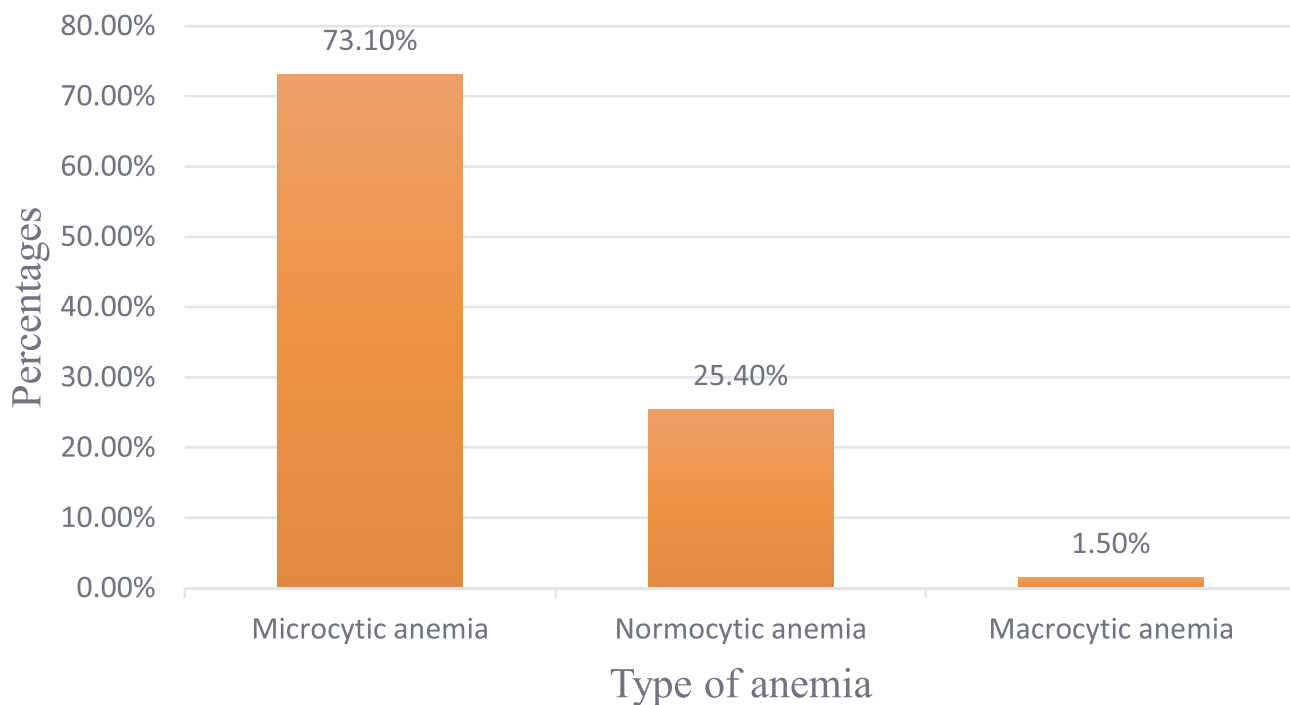


Figure 2 Type of anemia among undernourished under-five children, University of Gondar Specialized Referral Hospital, 2020.

The magnitude of anemia in this study (53.4% (95% CI: 47.2–59.6)) was in line with similar studies done in Sri Lanka (55.5%)⁴² and Bangladesh (56.5%).⁴³ However, it was lower than studies done in Ethiopia (61% in stunted, 64.3% in underweighted, and 68.2% in wasted children),¹⁷ India (84%,⁴⁴ 90%,⁴⁵ 91%,⁹ and 95%²²), and Brazil (88%).⁴⁶ In contrast, it was higher

than study conducted in Ethiopia (41.43%).⁴⁷ The possible explanation for the difference could be attributed to variations in the socio-demographic characteristics, sample size, and study design. The high intensity of parasitic infections and non-regular consumption of vegetables and fruits might partly explain the high magnitude of anemia in this study.

Table 4 Logistic Regression Analyses of Anemia and Explanatory Variables Among Undernourished Under-Five Children Attending at the University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020

Variables	Category	Anemia		COR (95% CI)	AOR (95% CI)
		Yes N (%)	No N (%)		
Gender	Male	74(58.7)	52(41.3)	1.54(0.94–2.54)	1.99(1.10–3.61)*
	Female	60(48)	65(52)	1 ^a	1 ^a
Age (months)	6–23	98(64.9)	53(35.1)	4.37(2.01–9.54)	5.45(2.13–13.93)*
	24–35	18(47.4)	20(52.6)	2.13(0.83–5.50)	1.75(0.61–5.03)
	36–47	7(28)	18(72)	0.92(0.30–2.83)	0.43(0.23–2.74)
	48–57	11(29.7)	26(70.3)	1 ^a	1 ^a
Residence	Rural	76(64.4)	42(35.6)	2.34(1.41–3.90)	1.65(0.67–4.06)
	Urban	58(43.6)	75(56.4)	1 ^a	1 ^a
Maternal educational status	No formal education	75(61.5)	47(35.8)	2.31(1.14–4.66)	1.27(0.26–6.14)
	Primary education	41(48.2)	44(51.8)	1.35(0.65–2.81)	1.08(0.29–3.91)
	Secondary & above	18(40.9)	26(59.1)	1 ^a	1 ^a
Paternal educational status	No formal education	61(62.2)	37(37.8)	2.37(1.24–4.56)	0.71(0.16–3.27)
	Primary education	48(52.2)	44(47.8)	1.57(0.82–3.02)	0.78(0.23–2.71)
	Secondary & above	25(41)	36(59)	1 ^a	1 ^a
Maternal occupational status	House wife	111(55.8)	88(44.2)	1.009(0.263–3.870)	–
	Gov't employee	11(37.9)	18(62.1)	0.489(0.108–2.221)	–
	Daily laborer	7(50)	7(50)	0.800(0.149–4.297)	–
	Private	5(55.6)	4(44.4)	1 ^a	–
Paternal occupational status	Farmer	70(64.8)	38(35.2)	2.76(1.39–5.51)	2.04(0.66–6.33)
	Gov't employee	21(37.5)	35(62.5)	0.90(0.41–1.97)	0.83(0.32–2.15)
	Daily laborer	23(62.2)	14(37.8)	2.46(1.03–5.90)	3.12(1.14–8.55)*
	Private	20(40)	30(60)	1 ^a	1 ^a
Birth order	First	45(51.7)	42(48.3)	1 ^a	1 ^a
	Second	30(43.5)	39(56.5)	0.72(0.38–1.36)	1.10(0.53–2.41)
	Third	23(48.9)	24(51.1)	0.89(0.44–1.82)	1.07(0.45–2.53)
	Fourth and above	36(75)	12(25)	2.80(1.29–6.09)	3.01(1.20–7.54)*
Diarrhea	Yes	80(58)	58(42)	1.51(0.92–2.49)	0.98(0.52–1.86)
	No	54(47.8)	59(42.2)	1 ^a	1 ^a
Fever	Yes	83(58.9)	58(41.1)	1.66(1.00–2.74)	1.67(0.89–3.15)
	No	51(46.4)	59(53.6)	1 ^a	1 ^a
Intestinal parasite	Yes	28(65.1)	15(43.9)	1.80(0.91–3.56)	2.87(1.25–6.63)*
	No	106(51)	102(49)	1 ^a	1 ^a
Edema	Yes	11(78.6)	3(21.4)	3.39(0.80–12.49)	5.33(1.20–23.56)*
	No	123(51.9)	114(48.1)	1 ^a	1 ^a
Meat consumption	Yes	34(42)	47(58)	1 ^a	1 ^a
	No	100(58.8)	70(41.2)	1.98(1.16–3.38)	1.03(0.48–2.21)
Vegetable and fruit intake	Yes	48(41.7)	67(58.3)	1 ^a	1 ^a
	No	86(63.8)	50(36.8)	2.40(1.44–3.99)	2.05(1.03–4.10)*
Cereal foods intake	Yes	88(49.4)	90(50.6)	1 ^a	1 ^a
	No	46(63)	27(37)	1.74(0.99–3.05)	1.13(0.52–2.41)

Notes: 1^a indicates reference category, *Indicates statistically significant at level of P < 0.05.

Abbreviations: AOR, adjusted odd ratio; COR, crude odd ratio; CI, confidence interval.

Table 5 Bivariable and Multivariable Analyses of Socio-Demographic, Clinical, and Feeding Characteristics as Predators of Leukocytosis Among Undernourished Under-Five Children Attending at the University of Gondar Specialized Referral Hospital, Northwest Ethiopia, 2020

Variable	Category	Leukocytosis		COR 95% CI	AOR 95% CI
		Yes N (%)	No N (%)		
Gender	Male	30(23.8)	96(76.2)	0.74(0.43–1.30) 1 ^a	–
	Female	37(29.6)	88(70.4)		
Age (month)	6–23	41(27.2)	110(72.8)	2.39(0.87–6.54)	1.94(0.66–5.71)
	24–35	10(26.3)	28(73.7)	2.29(0.69–7.49)	1.96(0.57–6.72)
	36–47	11(44)	14(56)	5.10(1.47–17.19)	4.05(1.13–14.55)*
	48–59	5(13.5)	32(86.5)	1 ^a	1 ^a
Birth order	First	25(28.7)	62(71.3)	1.36(0.59–3.07)	–
	Second	19(27.5)	50(72.5)	1.28(0.54–3.01)	–
	Third	12(25.5)	35(74.5)	1.15(0.452.95)	–
	Fourth	11(22.9)	37(77.1)	1 ^a	–
Diarrhea	Yes	38(27.5)	100(72.5)	1.10(0.63–1.93) 1 ^a	–
	No	29(25.7)	84(74.3)		
Fever	Yes	44(31.2)	97(68.8)	1.72(0.96–3.07) 1 ^a	1.80(0.92–3.53) 1 ^a
	No	23(20.9)	87(79.1)		
Intestinal parasite	Yes	13(30.2)	30(69.8)	1.24(0.60–2.54) 1 ^a	–
	No	54(26)	154(74)		
Edema	Yes	4(28.6)	10(71.4)	1.11(0.34–3.65) 1 ^a	–
	No	63(26.6)	174(73.4)		
Exclusive breast-feeding	Yes	54(25)	162(75)	1 ^a 1.77(0.84–3.76)	1 ^a 1.62(0.72–3.66)
	No	13(37.1)	22(62.9)		
Meat consumption	Yes	20(24.7)	61(75.3)	1 ^a 1.16 (0.64–2.14)	-
	No	47(27.6)	123(72.4)		
Milk intake	Yes	34(29.3)	82(70.7)	1 ^a 0.78(0.45–1.37)	-
	No	33(24.4)	102(75.6)		
Vegetable and fruit intake	Yes	28(24.3)	84(75.7)	1 ^a 1.25(0.71–2.19)	-
	No	39(28.7)	97(71.3)		
Cereal food intake	Yes	50(28.1)	128(71.9)	1 ^a 0.78(0.42–1.46)	–
	No	17(23.3)	56(76.7)		

Notes: 1^a indicates reference category, *Indicates statistically significant at level of P < 0.05.

Abbreviations: AOR, adjusted odd ratio; COR, crude odd ratio; CI, confidence interval.

The level of severity of anemia revealed that 44%, 38.8%, and 17.2% had mild, moderate, severe anemia, respectively. The magnitude of severe life-threatening anemia in the current study was comparable to the results of the studies reported from Nigeria (24%),³⁰ India (19%)²⁸, and Turkey (17.6%).¹⁶ However, it was higher than the study done in Sri Lanka (0.7%)⁴² while, it was lower than studies conducted in India (67% and 52%) of the participants had severe anemia.^{22,45} The difference might be variations in socio-demographic characteristics of the study participants, sample size, study design, and study period. Besides, it may also be

related to variation in the local prevalence of parasitic infections (hookworms and malaria) and dietary habits.

Morphological classification of anemia showed that 73.1% had microcytic anemia followed by normocytic anemia (25.4%). Similarly, a study done in India showed that microcytic anemia (55%) was the predominant type of anemia in undernourished children.⁴⁴ In contrast, Dwivedi et al reported that macrocytic anemia was the most common type of anemia in children with SAM.²⁸ The depletion of iron is the possible reason for the high percentage of microcytic anemia.⁴⁸

In the current study, the second common hematological abnormalities were leukocytosis, which was observed in 26.7% (95% CI: 21.2–32.20). Even though the percentage of leukocytosis is not reported, different studies confirm that leukocytosis a common feature in undernourished children. Findings from previous studies in India,^{9,22} Nigeria,³⁰ and Sudan²⁷ showed that the mean value of WBC count was higher in undernourished children when compared with their counterparts. The reason for the increment of leukocyte count may be related to infections like gastroenteritis and respiratory tract infections which are commonly seen in PEM.^{9,49} On the other hand, leukopenia occurred in 2.8% (95% CI: 0.74–4.8) of the study participants. A similar finding has been reported previously in several studies.^{28,50,51} Experimental studies suggest that leukopenia in malnutrition occurs due to the spleen and bone marrow hypoplasia which compromise hematopoiesis.⁵² This may cause immune suppression and increase susceptibility to infection. As Dwivedi et al state leukopenia may also be attributed to vitamin B12 deficiency in children with acute malnutrition.²⁸

An increment of platelet count was observed in 23.9% (95% CI: 18.59–29.22) of the children. Similar studies were done in Turkey,³¹ India,⁹ and Sudan²⁷ reported that higher mean platelet count in children with malnutrition. The possible reason for thrombocytosis during malnutrition may be associated with infection. For example during respiratory tract infection, there are increasing levels of inflammatory cytokines which heightens the production of thrombocytes.³³ In contrast, thrombocytopenia was observed by 8% (95% CI: 4.59–11.34). The decrement of platelet count in the current study was in agreement with previous studies.^{22,30,31} The possible reason for the decrement of platelet count in undernourished children attributed to a decrease in BM activities and platelet destruction during infection.^{30,31}

In this study, a child whose ages between 6 and 23 months was found to be 5.45 times more prone to anemia as compared to an older age counterpart (AOR= 5.45; 95% CI (2.13–13.93)). This is in line with studies done in Bangladesh⁴³ and Sri Lanka.⁴² The possible reason for the high magnitude of anemia in this age group may be related to the low concentration of iron in breast milk which is insufficient to meet the daily iron requirements of the child.⁵³ Being male in gender and being fourth and above in birth order were also associated with anemia in this study (AOR= 1.99; 95% CI: 1.10–3.61) and (AOR= 3.01; 95% CI: 1.20–7.54) respectively. This is similar to studies done in India.^{54,55} The possible explanation could

be due to state of the rapid growth of male children in the first months of life which increases their micronutrient requirement including iron.^{56,57} Increasing birth order increases the anemic status of the children. This may be related to maternal depletion of micronutrients which have few significant effects on the iron status of the newborn.⁵⁵

Children being infected by intestinal parasites are 2.87 times more likely to have anemia than children who are free from parasitic infection (AOR= 2.87; 95% CI: 1.25–6.63). It is in agreement with similar study done in India.⁵⁸ The reason might be intestinal parasites suck blood and also damage the intestinal wall, causing blood leakage. It may also relate to the parasite directly induces iron deficiency through blood loss by mechanical rupture of host capillaries and arterioles.⁵⁹ During infection or inflammation, there is a shortened cell survival, impaired response to erythropoietin, and impaired iron availability due to inadequate release of iron by the reticuloendothelial cells and reduced absorption from the gut.^{15,60} The other factor associated with anemia in undernourished children was edema (AOR= 5.33; 95% CI: 1.21–23.56). This might be related to excessive consumption of cow's milk that is frequently associated with iron deficiency and intestinal bleeding.^{61,62}

Not eating vegetables and fruits were found to be related to a risk of acquiring anemia (AOR= 2.05; 95% CI: 1.03–4.10). This may be related to fruits and vegetables serve as a good source of non-heme iron. Besides, Vitamin C which originates from fruits and vegetables potentiates absorption of non-heme iron that is found in legumes and other plant-based meals.⁶³ Also children whose paternal occupation is daily laborer are 3.13 more likely to have anemia than children whose father is a non-daily laborer (AOR= 3.13; 95% CI: 1.14–8.55). The reason might be children from poor households are less likely to get iron-rich foods.⁶⁴ On the other hand, children ages 36–47 months are 4.05 times more likely to develop leukocytosis (AOR= 4.05; 95% CI: 1.13–14.55). This might be children experience numerous infectious episodes in their childhood period.⁶⁵ Unlike anemia, thrombocytopenia and thrombocytosis were not significantly associated with explanatory variables. The possible explanation could be attributed to a small number of cases of children with these abnormalities and small sample size; therefore, the number of observations in each category of explanatory variables becomes small and these observations would have low power to predict association.

The present study had some limitations: Since the study design was cross-sectional, it is difficult to establish a cause–effect relationship between hematological abnormalities and associated factors as it is temporal association. Analyzing stool samples by direct wet mount technique potentially limits this study. Moreover, micronutrient deficiency such as iron, folate, and vitamin B12 which is a major predisposing factor for anemia was not assessed. The study does not screen children for sickle cell disease due to the unavailability of testing materials.

Conclusion and Recommendation

In the current study anemia was the major hematological abnormality identified, followed by leukocytosis and thrombocytosis. Anemia among undernourished under-five children is a severe public health problem in the study area. Child ages 6–23 months, being male, high birth order, father’s occupation (daily laborer), not eating vegetables and fruits, intestinal parasite infection, and edema was associated with anemia in undernourished children. On the other hand, only age of the child was associated with leukocytosis in undernourished under-five children. Therefore, improving the sanitation of children, deworming, food supplementation and strengthen and setting prevention programs, developing treatment protocols for anemia may help to reduce the burden of anemia, childhood mortality, morbidity, and its long-term implications. Moreover, case-control and longitudinal research are encouraged to see and describe the trend of hematological changes in undernourished children.

Abbreviations

AOR, adjusted odd ratio; CD, cluster of differentiation; CI, confidence interval; COR, crude odd ratio; EDTA, ethylene diamine tetra acetic acid; HAZ, height for age Z-score; Hb, hemoglobin; Hct, hematocrit; IQR, interquartile range; MCH, mean hemoglobin concentration; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; OR, odd ratio; PEM, protein energy malnutrition; RBC, red blood cell; SAM, severe acute malnutrition; SD, standard deviation; WAZ, weight for age Z-score; WBC, white blood cell; WHO, World Health Organizations; WHZ, weight for height Z-score.

Data Sharing Statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The study was approved by the Ethical Review Committee of the School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar. The study was also done as per the declaration of Helsinki.

Acknowledgments

We would like to acknowledge University of Gondar, College of Medicine and Health Sciences, School of Biomedical and Laboratory Sciences, Department of Hematology and Immunohematology for their financial support to conduct the study. We would like to thank children and their parents/guardians for their willingness to participate in this study. Finally, our special thanks goes to laboratory and nutritional rehabilitation center nursing staff members of the University of Gondar Specialized Referral Hospital for their cooperation during data collection.

Author Contributions

All authors made substantial contributions to conceptualization and design, data acquisition, data analysis and interpretation, took part in drafting of the initial manuscript and revising it critically for final approval of the version to be published. All authors agreed to submit to the current journal and agreed to be accountable for all aspects of the work.

Funding

University of Gondar.

Disclosure

The authors declare that they have no conflicts of interest.

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