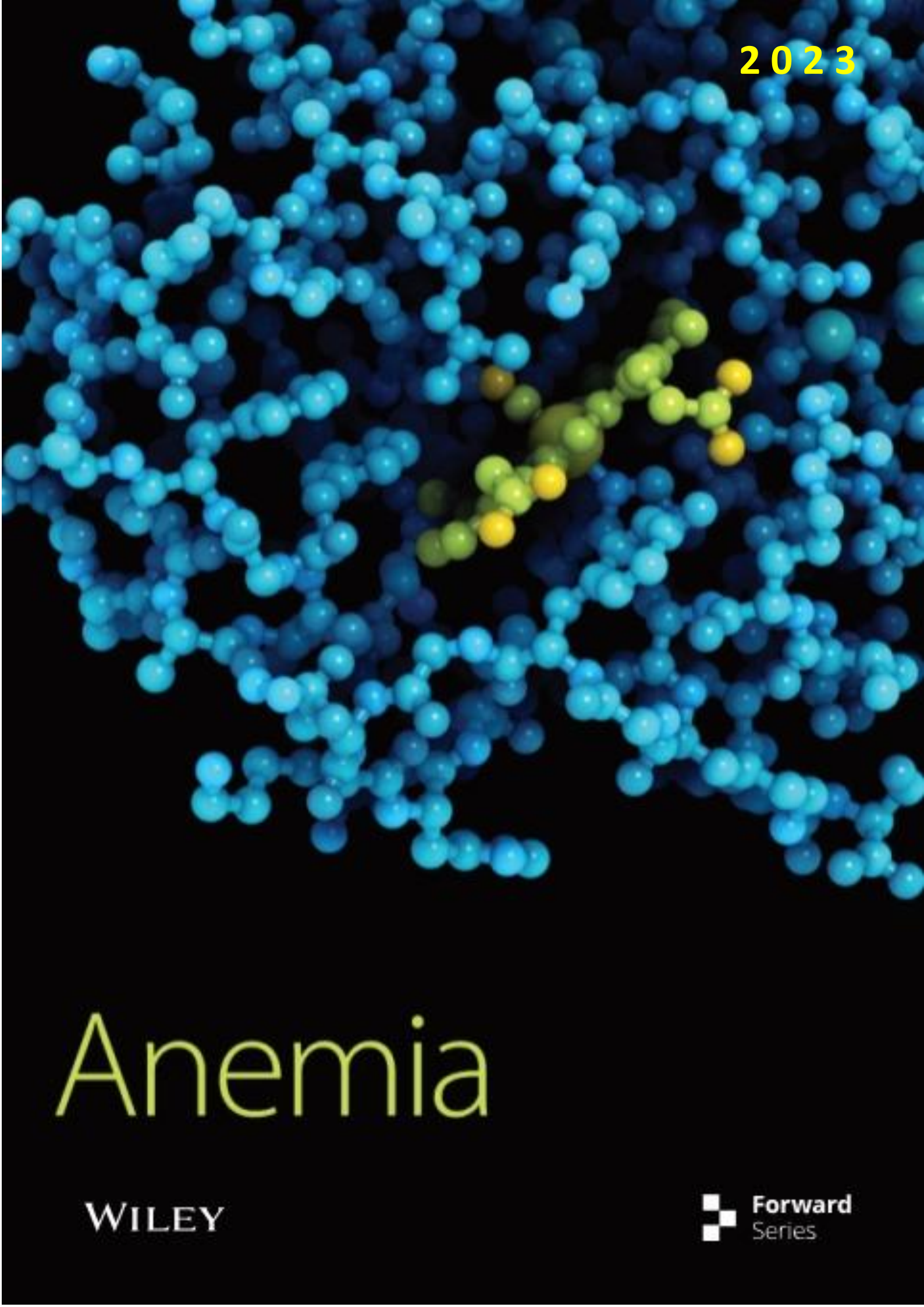

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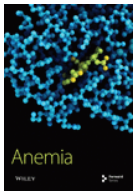

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Research Article

Prevalence of Iron Deficiency, Anemia, and Associated Factors in a Blood Donor Population in Brazzaville, Congo

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Introduction. Blood donation is not without risk to the donor. It results in a substantial loss of iron and decreased hemoglobin. In our country, no predonation assessment is carried out and the selection of blood donors is only clinical. *Objectives*. To determine the prevalence of iron deficiency, anemia, and iron deficiency anemia and to identify the factors associated with anemia and iron status in a blood donor population at the National Center for Blood Transfusion (NCBT). *Methodology*. A prospective study is carried out that consists of 120 blood donors in three NCBT branches in the capital from June to November 2021. The donors were divided into 3 groups: first time donors (FTDs), occasional donors (ODs) who have already made between 1 and 3 previous donations, and regular donors (RDs) with at least 4 previous donations. Iron deficiency was defined by a serum ferritin value of less than 30 ng/mL in men and 20 ng/mL in women. Anemia was defined by Hb levels below 13 g/dL in men and 12 g/dL in women. Iron deficiency anemia was defined by association of anemia and iron deficiency. The chi-square test was used for the comparison of the proportions. The odds ratio with the 95% confidence interval was calculated to assess the association between two variables. The p value of the probability was considered significant for a value < 0.05. *Results*. Mean serum ferritin and hemoglobin values were lower in RD in both sexes. The prevalence of iron deficiency, anemia, and iron deficiency anemia were 16.66%, 31.66%, and 10.83%, respectively. The factors associated with the three abnormalities were female sex, donor type, including RD, and number of previous donations. *Conclusion*. Iron deficiency, anemia, and iron deficiency anemia are common among blood donors in Brazzaville. Anemia affects almost a third of blood donors and is not always linked to iron deficiency. Safety of donors should be improved by systematic measurement of ferritinemia and hemoglobin levels before allowing donations for appropriate management in the event of abnormalities.

1. Introduction

Blood transfusion is an essential replacement therapy for many patients during various medical and surgical conditions. Transfusions of erythrocyte concentrates are performed in dozens as part of intensive oncology treatment, chronic anemia, a severe hemorrhagic accident, or an organ transplant. Blood donation is regulated by regulations whose purpose is, on the one hand, to guarantee the safety of blood transfusions made by blood products derived from these donations and, on the other hand, to preserve the health of donors. To reduce the infectious risk of transfusion, WHO recommends the use of voluntary but regular blood donors. Thus, they constitute a population at risk of iron deficiency and of anemia [1, 2]. Blood donation results in a substantial loss of iron and a decrease of approximately 1 g/dL in

hemoglobin (Hb) with each collection procedure, during which up to 425 to 475 ml of total blood is collected [3, 4].

To prevent these risks and avoid inappropriate donations, a number of strategies are being implemented by some teams, including limiting the annual number of blood donations and predonation screening for iron deficiency and anemia leading to deferral of blood donation below a certain threshold of eligibility for blood donation [2, 5, 6]. In Africa, its practice is not systematic, and several studies have shown that iron deficiency and anemia in general are frequent and can affect, respectively, up to 63% and 36.5% of blood donors [7–11]. Furthermore, iron deficiency was the main but not exclusive cause of anemia. In the Republic of Congo, the practice of blood transfusion is important, and every year, more than 40,000 blood donations are made. These are preceded by a medical examination, including an interview aimed at screening for conditions that are contraindicative of donation and assessment of general health [12]. However, no hemoglobin and ferritinemia estimation is performed. Thus, in order to strengthen the safety of blood donors, we carried out this study, the first of its kind, whose objective was to determine the frequency of iron deficiency, anemia, and iron deficiency anemia in a population of blood donors and identify the associated factors.

2. Methodology

It was an analytical cross-sectional study that took place over a six-month period from June 1 to November 30, 2021. It was multicentric and was carried out in three of the four stations responsible for blood collection in Brazzaville, capital of the Republic of Congo: those of the teaching hospital, the specialized hospital Mère-Enfants Blanche Gomes, and the reference hospital of Makélékélé. Blood donors were recruited consecutively during the predonation interview. Those who met the eligibility criteria for blood donation, being between the ages of 18 and 60 years old, weighing 55 kg or more, and qualified by medical selection were selected for the study, having given their consent to participate. Those whose sampling process has not been completed due to difficulty in drawing blood and those whose determination of ferritinemia could not be carried out for hemolysed serum were excluded. The variables analyzed were sociodemographic (age, sex, type of donor, and number of previous donations) and biological (Hb level and ferritinemia). Three types of blood donors have been identified, all unpaid:

(i) *First-time donors (FTD)*. Donors who never had donated blood in the past

(ii) *Occasional donors (OD)*. Donors who have previously made between 1 and 3 donations in their lifetime regardless of the time between donations and/or since the last donation

(iii) *Regular donors (RD)*. Donors who have previously made at least 4 donations in their lifetime regardless of the time between donations and/or since the last donation

Table 1: Distribution of a population of blood donors by sociodemographic characteristics in Brazzaville, Congo.

Characteristics	*N* (120)	%
Sex		
Men	94	78.33
Women	26	21.67
Age (years)		
18–30	51	42.50
31–45	52	43.33
46–60	17	14.17
Type of blood donor		
RD*	29	24.17
OD**	08	06.67
FTD***	83	69.16

*Regular donors. **Occasional donors. ***First time donors: most of them (76/83) were recruited as part of a replacement blood donation still known as a compensation donation, when a family member or relative has received a blood product.

Before the total blood donation, 10 ml of blood was collected from a crease elbow vein: 5 ml on an EDTA tube for hemoglobin determination and 5 ml on a dry tube for ferritinemia. The analyses were carried out at the Faculty's Laboratory of Training, Research, and Analysis of Medical Biology of Health Sciences at Marien Ngouabi University in Brazzaville. The blood count was carried out on the HORIBA MEDICAL Yumizen H550 machine. The determination of ferritinemia was carried out using the Bio Mérieux mini vidas semiautomaton using the ELFA technique. Iron deficiency was defined by a ferritinemia value of less than 30 ng/mL in men and 20 ng/mL in women. Anemia was defined by a Hb level of less than 13 g/dL in men and 12 g/dL in women. Iron deficiency anemia was defined by association of anemia and iron deficiency.

The influence of the dependent variables was highlighted, thanks to the application of Fisher's exact test on our data. The statistical difference observed between the qualitative variables was assessed by the Pearson Khi2 test. The p value of the probability was considered significant for a value < 0.05.

3. Results

Table 1 shows the distribution of a population of blood donors by sociodemographic characteristics in Brazzaville, Congo.

The sex ratio was 4/1.

The average age was 34 years ± 10 years with extremes of 18 and 60 years.

Among the 26 women, there were 24 (92.31%) FTD, 02 (07.69%) RD, and no OD. Among the 94 men, there were 59 (62.77%) FTD, 27 (28.72%) RD, and 8 (8.51%) OD. The median value of ferritinemia in blood donors was 74.03 ± 16.74 ng/mL. It was 88.46 ± 14.76 ng/mL ± in men and 53.08 ± 22.94 ng/mL ± in women. The median Hb value was 13.80 ± 2.81 g/dL. It was 14.25 ± 1.94 g/dL in men and 11.70 ± 4.58 g/dL in women.

Table 2: Mean values of ferritinemia and Hb levels in a blood donor population by the blood donor type and sex in Brazzaville, Congo.

	Men		Women	
	Mean	Max/Min	Mean	Max/Min
Ferritinemia (ng/mL)				
RD*	64.82	1200.00/07.26	45.70	1200.00/09.52
OD**	98.81	348.08/10.19	—	—
FTD***	152.81	197.97/03.21	104.88	57.05/34.35
Hb (g/dL)				
RD*	13.18	16.90/08.40	09.95	11.70/08.20
OD**	14.40	15.60/10.10	—	—
FTD***	14.60	17.80/09.20	12.66	25.00/06.60

*Regular donors. **Occasional donors. ***First time donors.

Table 2 presents the mean values of ferritinemia and Hb levels in a blood donor population by the blood donor type and sex in Brazzaville.

Table 3 shows the prevalence of iron deficiency, anemia, and iron deficiency anemia in a blood donor population in Brazzaville, Congo.

Among the 20 blood donors with iron deficiency, 13 or 65% were in the anemia stage and the remaining 7 were in the preanemic stage.

Concerning the 38 blood donors who had anemia, it was linked to iron deficiency in 13 cases (34.21% of anemia). Anemia was therefore undetermined in 65.79%.

Table 4 shows the correlation between the presence of iron deficiency, anemia, and iron deficiency anemia in blood donors and the sex, type of donor, and number of previous blood donations.

4. Discussion

The male predominance of blood donors (78.33% of cases) observed in our study is common in sub-Saharan Africa, as shown by several studies: 79.9%, 80.6%, and 89.3%, respectively, in Nigeria [13], DRC [8], and Ghana [10], up to 95.1% in our country [12]. These high proportions could be explained among other things by the contraindications of blood donation that are numerous in women, especially breastfeeding, menstruation, or pregnancy less than 6 months old. However, cultural causes should be sought, since studies carried out in Western countries report almost equal proportions of male and female blood donors [6, 14] more globally; WHO reports that 33% of blood donations come from women [1].

The majority of blood donors in our country remain replacement donors as reported in a previous 10-year study [12]. With a shortage of blood products in the country, families often have no choice but to donate replacement blood and hope to benefit from a blood product in the future. According to WHO data, of the 118.5 million blood donations collected annually worldwide, 40% are collected in high-income countries, where 16% of the world's population lives. There are 31.5 blood donations per 1,000 population in high-income countries, compared to 5.0 in low-income countries, which still collect more than 50% of their blood supply through offsetting or paid donations [1].

Table 3: Prevalence of iron deficiency, anemia, and iron deficiency anemia in a blood donor population in Brazzaville, Congo.

Parameters	*N* (120)	%
Iron deficiency		
Yes	**20**	**16.66**
No	100	83.34
Anemia		
Yes	**38**	**31.66**
No	82	68.34
Iron deficiency anemia		
Yes	**13**	**10.83**
No	107	89.17

The design limitation in our study is the fact that the subclinical inflammation using at least CRP was not screened, knowing that ferritin is an acute phase protein and will be artificially increased by inflammation. This is apparent in the results since ferritin levels were as high as 1200 ng/mL in some participants which is indicative of either inflammation, and/or iron overload. It also implies that the prevalence estimated for iron deficiency or iron deficiency anemia might not reflect the true picture in the study population since some iron-deficient individuals might have been qualified as not being iron-deficient.

Iron deficiency in blood donors is a global problem [3, 8, 14–19]. The frequency found in our series, of 16.66%, seems low compared to those reported in Africa: 17.5% in a large population of nearly 4,500 blood donors in South Africa [15], 20.6% in Nigeria [16], just over a quarter (27.4%) in Ghana [10], 35.2% in Algeria [9], or 63% in the DRC [8] to name but a few. But, as suggested above, the hemoglobin estimation might have been adversely affected by the absence of subclinical inflammation screening; therefore, anemia prevalence might have been underestimated. In the last two studies, the high proportions of iron deficiency could be explained by the fact that regular blood donors were the most numerous and the prevalence of iron deficiency was higher among these regular donors than among other types of donors. In lesser developed countries where iron deficiency is already a public health problem, the prevention of anemia in general and iron deficiency anemia, in particular, must be an essential issue for the safety of the blood donor but also for quantitative and qualitative self-sufficiency in blood products. Indeed, iron deficiency can be the cause of anemia with multiple clinical implications in relation to the decrease in oxygen transport in the body.

This prevention is based, on the one hand, on the postponement of donors whose Hb level is below a regulatory threshold and, on the other hand, on the prevention of iron deficiency. Several measures can be used: the increase in the minimum interval between two total blood donations and/or the reduction in the maximum annual frequency of donations; the assay of serum ferritin measuring iron reserves and finally donor iron supplementation [2, 17, 18, 20–22]. In France, after modeling different scenarios measuring the loss of donations, it was decided to opt for a ferritinemia strategy directed at groups at risk of iron deficiency with postponement of 6 months if ferritinemia

Table 4: Correlation between the presence of iron deficiency, anemia, and iron deficiency anemia in blood donors and the sex, type of donor, and number of previous blood donations.

	Iron deficiency	OR	95% IC	*p*
Sex				
Male ($n = 94$)	13.83%			
Female ($n = 26$)	23.08%	1.8692	0.6322–5.5269	0.003
Type of donor				
RD* ($n = 29$)	27.58%	0.8750	0.1453–5.2702	0.04
OD** ($n = 8$)	25%			
FTD*** ($n = 83$)	10.84%	0.3649	0.0638–2.0861	0.03
Number of previous donations				
0–3 ($n = 93$)	11.83%			
4 and more ($n = 27$)	29.63%	0.3186	0.1128–0.9000	0.02
	Anemia	OR	95% IC	*p*
Sex				
Male ($n = 94$)	25.53%	3.9773		
Female ($n = 26$)	57.69%		1.6078–9.8384	0.000
Type of donor				
RD* ($n = 29$)	44.82%	1**2308	0**2567–5**8999	0.03
OD** ($n = 8$)	50%			
FTD ($n = 83$)	25.30%	0.3607	0.0830–1.5672	0.007
Number of previous donations				
1–3 ($n = 93$)	27.96%			
4 and more ($n = 27$)	48.15%	0.4179	0.1733–1.0079	0.04
	Iron deficiency anemia	OR	95% IC	*p*
Sex				
Male ($n = 94$)	7.44%			
Female ($n = 26$)	23.077%	3.7286	1.1299–12.303	0.002
Type of donor				
RD* ($n = 29$)	13.79%	2.0833	0.3063–14.1687	0.04
OD** ($n = 8$)	25%			
FTD*** ($n = 83$)	8.43%	0.2763	0.0467–1.6348	0.07
Number of previous donations				
0–3 ($n = 93$)	9.68%			
4 and more ($n = 27$)	14.81%	0.6161	0.1739–2.1826	0.453794

*Regular donors. **Occasional donors. ***First time donors.

<15 ng/ml and spacing of donations if between 15 and 25 ng/ml [17]. Regular monitoring of ferritinemia allows individualization of the blood donation calendar in Canada [23]. In the face of the ongoing challenge of the blood supply facing many African countries [1, 24], it is not easy to address the problem of iron deficiency and anemia in front-line blood donors and reach a consensus. Some experts oppose systematic substitution treatment after donation, fearing to mask an iron deficiency not related to the donation [17]. Determining suitability for donation through isolated dosing of Hb prior to donation would at least not aggravate preexisting anemia.

In our study, nearly, a third of donors had anemia (31.66%) of which 34.21% were iron-deprived, confirming some observations that iron deficiency accounts for a significant share of anemia in blood donors, especially the most regular [25–27]. More than 65% of the anemia is not being attributed to iron deficiency. This high proportion of anemia illustrates the need for a predonated biological assessment to diagnose, explore, and adequately manage potential future donors. Throughout the world, the most common cause of anemia is martial deficiency, due to prolonged deficiency resulting from inadequate dietary iron intake, increased requirements during growth or pregnancy, and increased losses due to menstruation or helminthiasis. In Africa, and more particularly in tropical zones, apart from genetic causes (especially sickle-cell anemia), other important causes include infections and nutritional deficiencies in folic acid and vitamin B12. In areas of high prevalency, anemia is an important complication of malaria [28, 29]. Blood donor management should be comprehensive, addressing both nutritional and non-nutritional causes of anemia as appropriate.

Factors associated with iron deficiency on the one hand, and with anemia and iron deficiency anemia on the other hand, were, respectively, the number of donations (especially after the third) and the female sex. These are factors traditionally reported in the literature [6, 7, 9, 17, 25, 30]. In the Nzengu-Lukusa study in the Democratic Republic of Congo, iron deficiency was associated with the male sex: 70.42% in men compared to 33.33% in women. This may be due to the fact that family donors were not included in the study and regular donors are primarily male [8].

5. Conclusion

Iron deficiency, anemia, and iron deficiency anemia are common among blood donors in Brazzaville, especially among women and RD. In addition, the risk increases with the number of donations. The safety of donors should be improved by simple measures such as systematic measurement of ferritinemia and measurement of Hb levels prior to allowing donations. This predonation screening of iron deficiency and anemia will make it possible to carry out an etiological survey and then a curative and preventive management adapted to the different causes.

Data Availability

The data used to support the findings of this study are included within the article.

Ethical Approval

Ethical approval number 374/MESRSIT/IRSSA-CERSSA for the study was obtained from the National Health Science Research Ethics Committee.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Burden of Anemia among Human Immunodeficiency Virus-Positive Adults on Highly Active Antiretroviral Therapy at Hawassa University Compressive Specialized Hospital, Hawassa, Ethiopia

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Background. Anemia is the most common hematologic abnormality associated with human immunodeficiency virus (HIV)-infected patients and affects 60% to 80% of patients in late-stage disease. It has a considerable impact on the progression of HIV to advanced stages. This study aimed at assessing the burden of anemia in adult HIV-infected patients who are on highly active antiretroviral therapy (HAART) and have follow-up at Hawassa University Comprehensive Specialized Hospital (HUCSH) Antiretroviral therapy (ART) clinic. *Methods*. A hospital-based retrospective study was conducted among HIV-positive adults on HAART at Hawassa University Compressive Specialized Hospital. The systematic sampling method was used to choose a total of 244 study participants. Data on demographic characteristics, related factors of anemia, latest hemoglobin, CD4, and ART regimens were collected using a structured data abstraction format. The data were cleaned and analyzed using SPSS version 21.0 after being manually checked for completeness. Multivariable logistic regression was carried out to detect elements associated with anemia. A P value of <0.05 was used as a cutoff point to announce statistical significance. *Results*. The records of 244 patients were examined in total. Anemia was present in 29.9% (95% CI 23.8–35.2) among adult HIV patients. Female sex (AOR: 2.576, 95% (CI: 1.295–5.127)), having tuberculosis (TB) (AOR: 4.873, 95% (CI: 1.534–15.484)), taking a zidovudine (ZDV)-containing ART regimen (AOR: 5.216, 95% (CI: 1.239–21.962)), having clinical WHO stage IV and III diseases (AOR: 3.077, 95% CI (1.244–7.612)), having body mass index (BMI) <18.5 kg/m^2 (AOR: 2.391, 95% (CI: 1.138–5.023)), and taking cotrimoxazole prophylaxis (AOR: 3.860 95% (CI: 1.097–13.576)) were substantially linked to the development of anemia among adult HIV patients. *Conclusion and Recommendation*. This study showed that anemia is still a problem among HIV patients on HAART. The burden of anemia was found to be high among patients with advanced WHO clinical stages, having a BMI less than 18.5 kg/m^2, TB/HIV coinfection, being on AZT-based ART regimens, and taking cotrimoxazole preventive therapy (CPT). Consequently, it is suggested that early preventative interventions, such as serial hemoglobin follow-up, iron supplementation, and education about dietary consumption, be undertaken targeting the aforementioned groups. In addition, the preferred first-line ART regimen as per the latest national and WHO guidelines is recommended, especially for the above groups.

1. Introduction

The human immunodeficiency virus (HIV) is a virus that affects the human immune system and puts the infected person at risk of opportunistic infections. Acquired immunodeficiency syndrome (AIDS) is the late stage of the disease. The current 2021 UNAIDS Ethiopia Spectrum national PLHIV estimate is 616,105 [1].

Hematological abnormalities manifested by pancytopenia are among the most common manifestations of HIV/AIDS, with anemia being the leading abnormality [2–4]. Anemia is a state characterized by a decreased quantity of red blood cells that is not enough to meet the body's physiological requirements [5]. However, the distribution of anemia in HIV patients varies significantly, ranging from 1.3% to 95% [6]. There are a lot of factors, including stage of HIV, age, and sex, which are said to account for the variations in the distribution of anemia in HIV-infected individuals [6]. Direct effects of the virus on bone marrow, medication related, poor intake result in nutritional deficiency, and anemia of chronic illnesses are common reasons [7, 8]. Normocytic normochromic anemia is the most encountered morphologic type of anemia in HIV, followed by microcytic hypochromic and macrocytic anemia [9, 10]. Anemia of chronic disease is the most common cause of normocytic normochromic and microcytic hypochromic anemia in HIV-infected individuals, and iron deficiency anemia is a relatively infrequent cause of microcytic hypochromic anemia [9]. The natural course of HIV disease influenced by anemia increases the rate of disease progression to advanced stage and increase mortality [11]. Severe anemia is associated with a faster rate of HIV disease progression. They have also demonstrated that anemia is an important indicator of death among HIV patients. Untreated anemia can exacerbate poverty in areas with a high HIV incidence and cause a variety of systemic consequences such as fatigue, exhaustion, a higher risk of HIV dementia, poor quality of life, and more [12]. On the other hand, survival time in HIV-infected persons may be improved after recovery from anemia [13]. Globally, anemia is a major health problem that can cause poor quality of life, morbidity, and death and affects the socioeconomic development of a nation. It has a greater impact on developing countries than on developed countries [14].

Despite the fact that low level of red blood cell mass is a major cause of morbidity and mortality in patients with HIV/AIDS, data on anemia and associated risk factors among RVI patients are generally insufficient from low-resource countries such as Africa, including Ethiopia. It is still a common problem among patients taking ART, so early identification and interventions to correct anemia may lead to improved health and survival potential of HIV-infected people. Identification and correction of associated factors will help to prevent the development of anemia, which in turn will improve the quality of life and survival of HIV/AIDS patients.

We conducted this study to determine the burden of anemia among adult HIV patients receiving ART at the ART clinic at Hawassa University Comprehensive Specialized Hospital because, to the best of our knowledge, there are no published data on this topic in the study area.

2. Methods

2.1. Study Setting and Period. The study was carried out at Hawassa University Comprehensive Specialized Hospital, Hawassa City, Sidama Region, Ethiopia. Hawassa University Comprehensive Specialized Hospital provides HIV/AIDS interventions, including free diagnosis, treatment, and follow-up. ART clinic is a major unit under the department of internal medicine. It was established in the hospital in 1997, E.C., and since then the hospital has provided ART services to 7965 clients. Among this group, there are 2,802 currently active adult clients on ART. The center diagnoses new cases and follows those on therapy. Structured HIV/AIDS data are available at this specialized hospital.

This study was carried out from August to December 2021 to search for the burden of anemia among people with HIV/AIDS who are on ART at HUCSH.

2.2. Study Design. A facility-based retrospective cross-sectional study was conducted among HIV-positive adults at the ART follow-up clinic of HUCSH.

2.3. Source Population. Source population includes all HIV-positive patients above the age of 18 years having follow-up at ART clinic at Hawassa University Comprehensive Specialized Hospital.

2.4. Study Population. Study population includes all HIV positive patients above the age of 18 years on ART who had follow-up at ART clinic during the study period at Hawassa University Comprehensive Specialized Hospital.

2.5. Inclusion and Exclusion Criteria

2.5.1. Inclusion Criteria. The inclusion criteria were HIV-positive patients aged 18 years or older on ART, who have had regular follow-up and latest laboratory investigation (complete blood count (CBC) within 3 months and CD4 count within 6–12 months).

2.5.2. Exclusion Criteria. Patients transferred from other setups to the HUCSH ART clinic on their first visit, pregnant women and women in the postpartum period, and patients with incomplete information for hemoglobin (Hgb) status on the chart during follow-up were excluded from the study.

2.6. Sample Size Determination and Sampling Procedure

2.6.1. Sample Size Determination. A single population proportion formula was used to estimate the sample size with the following assumptions: prevalence of anemia after initiation of ART is 80.5% [15], the margin of error is 5%, and the confidence interval is 95% [15]. Therefore, the sample size required for this study was 244 patients.

2.6.2. Sampling Method. Among those adults attending the ART clinic at HUCSH during the study period, a total of 244 HIV-positive adults taking ART and on follow-up was selected by systematic sampling technique.

2.7. Data Collection Methods and Tools. The data were collected using a chart review by the nurses and physicians working in the ART clinic. A total of three health professionals, one ART nurse, one general practitioner as data collector, and one resident as supervisor from another unit, participated in the data collection process of this study. The information collected includes sociodemographics, clinical characteristics, and the immunohematology profile of patients. Data on the sociodemographic and clinical characteristics of the study participants were collected through a review of medical records. Weight and height measurements were taken from patients' charts, and BMI was calculated by dividing weight in kg by height in m^2. The BMI cutoff value according to WHO classification (in kg/m^2) was <18.5 (underweight), 18.5–24.99 (normal), 25–29.99 (overweight), and ≥30 (obese) [16].

2.8. Study Variables

2.8.1. Dependent Variable. Dependent variable is anemia.

2.8.2. Independent Variables

(1) Sociodemographic factors: age, sex, level of education, place of residence, occupation, marital status, and dietary intake
(2) WHO stage of HIV
(3) CD4+ T-cell count was taken from patient records and classified as <200 cells/μL, 200–500 cells/μL, and ≥500 cells/μL based on CDC
(4) Nutritional status (BMI)
(5) ART regimen

2.9. Operational Definitions

(1) Anemia is defined as hemoglobin (Hgb) concentration less than 13 g/dl for adult males and less than 12 g/dl for adult females [17, 18]
(2) Mild anemia is defined as Hbg 11–11.9 g/dl for women and 11–12.9 g/dl for men
(3) It is moderate (Hbg 8–10.9 g/dl) and severe (Hgb < 8 g/dl) for both sexes [14, 18]
(4) Microcytosis is defined as MCV <80 fL and macrocytosis is MCV >100 fl [18]
(5) Anemia prevalence cutoff values for public health significance include the following: <5%, no public health problem; 5–19%, mild public health problem; 20–39%, moderate public health problem; and ≥40%, severe public health problem [19]

2.10. Data Management and Analysis. The data were first checked manually for completeness and then entered and analyzed using SPSS version 21. Univariate analysis was used to summarize descriptive measures. Bivariate logistic regression analysis was used to identify candidate variables for multivariable logistic regression analysis. The multivariable analysis was conducted to control (adjust) for possible confounding variables. During the analyses, a P value <0.05 with 95% confidence interval (CI) for AOR (adjusted odds ratio) was used in judging the significance of the associations. Results were presented in text and tables.

2.11. Data Quality Control. To ensure the quality of the data, prior to data collection, training of the data collectors was carried out for one day by the principal investigator on the objective, relevance of the study, and confidentiality of information. The abstraction format was prepared in English for better understanding. The questionnaire was pretested with a 5% of sample size to learn about the appropriateness of the questions, which was conducted at the Adare General Hospital ART clinic, another public hospital in Hawassa City.

2.12. Ethical Considerations. Ethical clearance was obtained from the institutional review board of HUCSH. Then, permission was obtained from hospital management. After permission was obtained, data were collected from the ART clinic.

3. Result

3.1. Sociodemographic Characteristics. Out of two hundred forty-four patients reviewed, one hundred thirty-five (55.3%) of the study participants were females, of whom 21.7% were anemic, and the remaining, one hundred nine (44.7%) were males. Most participants, one hundred twenty-eight (52.4%), were in the age of 18–25 years.

Regarding the marital status of the participants, one hundred fifty-five (63.5%) were married, sixty-four (26.2%) were single, fifteen (6.1%) were divorced, and ten (4.1%) were widowed. The majority of participants, one hundred sixty-six (68%), were urban residents, and the rest seventy-eight (32%) were from rural areas. When it comes to the participants' religion, 117 patients (47.9%) were identified as orthodox, whereas eight (36%), twenty-three (9.5%), and sixteen (6.6%) were identified as protestants, Muslims, and others, respectively. Regarding their occupation, ninety-two (37.7%) were private workers and twenty-seven (11.1%), seventy-two (29.5%), and fifty-three (21.8%) were daily laborers, farmers, and government employees, respectively. In terms of educational attainment, thirty-three (13.5%), sixty-two (25.4%), seventy (28.7%), thirty-nine (16%), and forty (16.45) were illiterate, could read and write, and attended primary level, secondary level, and higher level education consecutively (Table 1).

Table 1: Socioeconomic and demographic characteristics of adult HIV patients on HAART at Hawassa university specialized hospital, 2021 ($n = 244$).

Background characteristics	Not anemic *N* (%)	Anemic *N* (%)	COR (95% CI)
Sex			
Male	89 (36.5%)	20 (8.2%)	Ref
Female	82 (33.6%)	53 (21.7%)	2.876 (1.586–5.217)
Age			
18–25	85 (34.8%)	43 (17.6%)	0.843 (0.192–3.695)
26–33	36 (14.8%)	14 (5.7%)	0.648 (0.136–3.081)
34–41	23 (9.4%)	10 (4.1%)	0.725 (0.144–3.634)
42–49	22 (9%)	3 (1.2%)	0.227 (0.35–1.477)
50 and more	5 (2%)	3 (1.2%)	Ref
Residency			
Urban	118 (48.45)	48 (19.7%)	1.160 (0.648–2.075)
Rural	53 (21.7%)	25 (10.2%)	Ref
Occupation			
Daily laborer	21 (8.6%)	6 (2.5%)	Ref
Farming	50 (20.5%)	22 (9%)	1.540 (0.546–4.342)
Private work	63 (25.8%)	29 (11.9%)	1.611 (0.588–4.416)
Gov. employee	37 (15.2%)	16 (6.6%)	1.514 (4.458)
Religion			
Protestant	63 (25.8%)	25 (10.2%)	Ref
Orthodox	83 (34%)	34 (13.9%)	1.032 (0.560–1.903)
Muslim	16 (6.6%)	7 (2.9%)	1.102 (0.405–3.002)
Others	9 (3.7%)	7 (2.9%)	1.960 (0.658–5.835)
Marital status			
Single	44 (18%)	20 (8.2%)	Ref
Married	108 (44.3%)	47 (19.3%)	0.957 (0.510–1.797)
Divorced	10 (4.1%)	5 (2%)	1.100 (0.332–3.640)
Widowed	9 (3.7%)	1 (0.4%)	0.244 (0.29–2.062)
Educational status			
Illiterate	23 (9.4%)	10 (4.1%)	Ref
Can read and write	42 (17.2%)	20 (8.2%)	1.095 (0.439–2.731)
Primary education	48 (19.7%)	22 (9%)	1.054 (0.430–2.587)
Secondary education	28 (11.5%)	11 (4.5%)	0.904 (0.326–2.502)
Higher level education	30 (12.3%)	10 (4.1%)	0.767 (0.273–2.150)

3.2. Baseline Clinical Characteristics. The large proportion of the study participants, two hundred ten (86.1%), was in WHO clinical stages of I and II, and the rest thirty-four (13.9%) were in WHO clinical stages III and IV. Two hundred thirty (94.3%) of the participants were taking non-AZT-containing regimen, and the remaining fourteen (5.7%) patients were on AZT-containing regimens.

About one hundred twenty (49.2%) of the study participants had a CD4 count of ≥500 cells/μL, and eighty-two (33.6%) and forty-two (17.2%) of the participants had a CD4 count between 200 and 500 cells/μL and a CD4 count below 200 cells/μL, respectively. Regarding tuberculosis, twenty-two (9.1%) of the study participants had a history of tuberculosis infection. About one hundred ninety (77.9%) of participants were not on cotrimoxazole and the remaining fifty-four (22.1%) were taking cotrimoxazole prophylactic therapy.

In terms of HIV duration from diagnosis, one hundred participants (41%) had HIV for 1–5 years, while fifty-seven (23.4%), forty-one (16.8%), and forty-six (18.8%) had HIV for 6–10 years, more than ten years, and 6 months to one year consecutively. Most patients, one hundred (41%) took ART for one to five years. The majority of patients, one hundred eighty-three (75%), had a body mass index of >18.5 kg/m^2, and the remaining sixty-one (25%) had ≤18.5 kg/m^2 (Table 2).

3.3. Magnitude of Anemia. Anemia was detected in 29.9% (95% CI 23.8–35.2) of HIV adult patients receiving ART. Thirty-three (13.5%), thirty-six (14.7%), and four (1.7%) of the patients had mild anemia, moderate anemia, and severe anemia, respectively. Thirty-four of these patients (13.9%) had normocytic anemia, thirty-three (13.5%) had macrocytic anemia, and six (2.5%) had microcytic anemia, according to the morphologic type of their anemia.

3.4. Factors Associated with Anemia among Adult HIV-Positive Patients. Bivariate logistic regression took into account a total of 15 variables, and 7 variables were included in the multivariable logistic regression model. Accordingly, females were three times more likely to develop anemia than males (AOR): 2.576, 95% CI (1.295–5.127). Participants with tuberculosis (TB) were five times more likely to develop

Table 2: Baseline clinical characteristics of adult HIV patients on HAART at Hawassa university specialized hospital, 2021 ($n = 244$).

Background characteristics	Not anemic *N* (%)	Anemic *N* (%)	COR (95% CI)
TB			
No	165 (67.6%)	57 (23.3%)	Ref
Yes	6 (2.5%)	16 (6.6%)	7.719 (2.882–20.679)
BMI			
>18.5	144 (59%)	39 (16%)	Ref
≤18.5	27 (11.1%)	34 (13.9%)	4.650 (2.509–8.616)
ART regimen			
Non-AZT-containing	168 (68.9%)	62 (25.4%)	9.935 (2.682–36.801)
AZT-containing	3 (1.2%)	11 (4.5%)	Ref
Duration of ART			
6 months–1 year	31 (12.7%)	17 (7%)	Ref
1–5 years	74 (30.3%)	26 (10.7%)	0.641 (0.305–1.345)
6–10 years	37 (15.2%)	18 (7.4%)	0.887 (0.392–2.008)
>10 years	29 (11.9%)	12 (4.9%)	0.755 (0.308–1.848)
Duration of HIV			
6 months–1 year	29 (11.9%)	17 (7%)	Ref
1–5 years	75 (30.7%)	25 (10.2%)	0.569 (0.268–1.204)
6–10 years	38 (15.6%)	19 (7.8%)	0.853 (0.378–1.924)
>10 years	29 (11.9%)	12 (4.9%)	0.706 (0.287–1.737)
WHO stage			
Stage I &II	154 (63.1%)	56 (23%)	Ref
Stage III & IV	17 (7%)	17 (7%)	2.750 (1.314–5.756)
Cotrimoxazole			
No	147 (60.2%)	43 (17.6%)	Ref
Yes	24 (9.8%)	30 (12.3%)	4.273 (2.264–8.066)
CD4 counts			
≥500	97 (39.8%)	23 (9.4%)	Ref
200–500	55 (22.5%)	27 (11.1%)	2.070 (1.084–3.954)
<200	19 (7.8%)	23 (9.4%)	5.105 (2.390–10.904)
Mean cell volume			
<70	10 (4.1%)	6 (2.5%)	Ref
70–100	84 (34.4%)	34 (13.9%)	0.675 (0.227–2.002)
>100	77 (31.6%)	33 (13.5%)	0.714 (0.240–2.127)

anemia than those who did not (AOR: 4.873, 95% CI (1.534–15.484)). Those patients on zidovudine (ZDV)-containing ART regimens were five times more likely to develop anemia than those on non-AZT-containing regimens (AOR: 5.216, 95% CI (1.239–21.962)).

Participants with clinical WHO stages III and IV were three times more likely to develop anemia than participants with clinical WHO stages I and II (AOR: 3.077, 95% CI (1.244–7.612)). Participants with a body mass indexes (BMIs) of less than or equal to 18.5 kg/m^2 were two times more likely to develop anemia than those having BMI of more than 18.5 kg/m^2 (AOR: 2.395 (1.138–5.023)). Patients who were on cotrimoxazole prophylactic therapy were four times more likely to develop anemia than their counterparts (AOR; 3.860, 95% CI (1.097–13.576)) (Table 3).

4. Discussion

The burden of anemia in our study (29.9% (95% CI 23.8–35.2)) is comparable with the findings of a similar study carried out in other areas (31.1% in the study conducted in Kambata, southern Ethiopia [20] and 26.2% in the study conducted in South Africa [21]). However, it is lower than that of studies conducted in other parts of the country: Zewidtu Memorial Hospital (42.9%) [20] and Tikur-Anbessa Specialized Hospital (41.9%) [21]. In addition, it was lower than the results of studies undertaken in other African countries: Ghana (63%) [2] and Tanzania (40.7%) [22]. The burden discovered in the current study, however, was higher than that of investigations carried out at Jimma University Hospital (16.2%) [23, 24] and in Malawi (16.2%) [14]. The disparities in the burden of anemia may be explained by the differences in the study area, study time, and health intervention measurement undertaken. Being a woman was highly related with anemia in the current study, which is consistent with the majority of other studies [4, 24] and reference [25]. Obstetric and gynecological conditions such as menstruation, pregnancy, and lactation may be the cause for this [14].

Another factor in the current study that is strongly linked to the burden of anemia is the use of ART medications that contain AZT. Studies carried out in Tanzania [22] and Kambata, South Ethiopia [25], backed up this conclusion. This is due to the fact that zidovudine suppresses erythroid stem cells, which inhibits the erythropoiesis process (red

Table 3: Factors associated with anemia among adult HIV patients on HAART at Hawassa university comprehensive specialized hospital, Hawassa, Ethiopia, 2021 ($n = 244$).

Characteristics	Anemia status			
	Not anemic *N* (%)	Anemic *N* (%)	COR (95% CI)	AOR (95% CI)
Sex				
Male	89 (36.5%)	20 (8.2%)	Ref	Ref
Female	82 (33.6%)	53 (21.7%)	2.876 (1.586–5.217)	2.576 (1.295–5.127)
ART regimen				
Non-AZT-containing	168 (68.9%)	62 (25.4%)	9.935 (2.682–36.801)	Ref
AZT-containing	3 (1.2%)	11 (4.5%)	Ref	5.216 (1.239–21.962)
TB				
No	165 (67.6%)	57 (23.3%)	Ref	Ref
Yes	6 (2.5%)	16 (6.6%)	7.719 (2.882–20.679)	4.873 (1.534–15.484)
BMI				
>18.5	144 (59%)	39 (16%)	Ref	Ref
≤18.5	27 (11.1%)	34 (13.9%)	4.650 (2.509–8.616)	2.391 (1.138–5.023)
WHO stage				
Stage I &II	154 (63.1%)	56 (23%)	Ref	Ref
Stage III & IV	17 (7%)	17 (7%)	2.750 (1.314–5.756)	3.077 (1.244–7.612)
Cotrimoxazole				
No	147 (60.2%)	43 (17.6%)	Ref	Ref
Yes	24 (9.8%)	30 (12.3%)	4.273 (2.264–8.066)	3.860 (1.097–13.576)

blood cell production) in the bone marrow and, as a result, lowers the generation of reticulocytes and hemoglobin levels [22].

This study discovered that having a WHO clinical stage III or IV considerably increased the risk of anemia, which is consistent with other studies carried out in Tanzania [22], Kamabata, south Ethiopia [25], and Zewidtu Memorial Hospital [20]. This is brought on by chronic inflammation and high viral replication that characterize the advanced stage of HIV. In other words, the high-viral load at the late stage of HIV causes defective hematopoiesis and altered coagulation processes, which cause the level of hemoglobin to decrease during this time and cause anemia to develop [26].

This study found that having tuberculosis increased the likelihood of anemia. Study reports from Kambata, south Ethiopia [25], and northwest Ethiopia [23] corroborated this conclusion. This is due to the immune system's reaction to tuberculosis, which causes the release of cytokines that impair the body's capacity to use both stored iron and iron obtained from nutrition, as well as the creation and regular function of the hormone erythropoietin. Anemia of chronic disease was the main cause for underlying anemia in HIV-TB coinfected patients [27].

Participants in this study were shown to have a higher risk of anemia if their BMI was under 18.5 kg/m^2. This result is consistent with study reports from Malawi, Kambata, south Ethiopia, and northwest Ethiopia [14, 23, 25]. A lower BMI indicates under nutrition as a result of insufficient calorie intake, poor nutrient absorption, or poor nutrient utilization, resulting in a deficiency of iron, folate, and vitamin B-12 for erythrocyte production. Furthermore, it increases the risk of infection, which increases the possibility of anemia [28].

This study discovered that cotrimoxazole use is connected with the development of anemia, which is consistent with similar study reports from the Ayder Mekelle specialized hospital [29] and study reports from Cote d'Ivoire [30]. The association between CPT and anemia may be explained by trimethoprim, a mild dihydrofolatereductase inhibitor that can limit folic acid metabolism and, at high doses, produce megaloblastic changes, especially in people who are not taking supplemental folate [31].

5. Limitations of the Study

This paper has its own limitations, such as the lack of information on dietary diversities, issues such as menstrual cycles, and workups for other causes of anemia. The social desirability bias, which we tried to minimize during data collection, was another limitation of our study.

6. Conclusion and Recommendation

This study showed that anemia is still a problem among HIV patients on HAART. The burden of anemia was found to be high among patients with advanced WHO clinical stages, having a BMI less than 18.5 kg/m^2, TB/HIV coinfection, being on AZT-based ART regimens, and taking cotrimoxazole preventive therapy (CPT). Consequently, it is suggested that early preventative interventions, such as serial hemoglobin follow-up, iron supplementation, and education about dietary consumption, be undertaken targeting the aforementioned groups. In addition, the preferred first-line ART regimen as per the latest national and WHO guidelines is recommended, especially for the above groups.

Data Availability

The data are fully available upon a reasonable request from the correspondent author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

All authors made significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data, participated in writing the article or critically revised it for important intellectual content, agreed to submit the article to the current journal, gave final approval of the version to be published, and agreed to be responsible for all aspects of the work.

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Research Article

Associated Factors of Cholelithiasis among Younger Children with Sickle Cell Disease at the National Reference Center for Sickle Cell Disease in Brazzaville, Congo

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Introduction. Chronic hemolysis predisposes sickle cell patients to the development of gallstones. Their frequency increases with age, but they may appear early in young children. In the absence of management, they expose the patient to complications that can hinder the quality of life and sometimes even death. This survey aimed to identify the associated factors of the occurrence of cholelithiasis. *Materials and Methods*. It was a case-control study carried out between January 2017 and June 2022 at the National Reference Center for Sickle Cell Disease (SCD) "Antoinette Sassou N'guesso" in Brazzaville. It concerned 37 children with cholelithiasis. Sociodemographic (socioeconomic status and diet) and clinical (body mass index, frequency of vasoocclusive crises and hospitalization for vasoocclusive crises, number of blood transfusion, and chronic complications) as well as hematological examination (type of SCD and blood count in the intercritical period) and hydroxyurea treatment were compared with those of 74 children with no clinical and radiographic signs of cholelithiasis. The chi-squared statistical test and the odds ratio were used for the comparison ($p < 0.05$). *Results*. The average age was 9.70 ± 1.73 years. The 10–12 age group was the most represented (22 cases or 59.45%), followed by 7- to 9-year-olds (12 cases or 32.43%). Three children (8.10%) were 6 years old. The sex ratio was 0.68 *vs.* 1.38. Factors associated with cholelithiasis were low socioeconomic status (83.78% *vs.* 45.95%; IC 95% 1.46–3.89; $p \leq 0.001$), a higher number of blood transfusions (5.54 ± 1.22 *vs.* 2.46 ± 1.13; IC 95% 1.55–6.70; $p \leq 0.001$), and irregular systematic monitoring (5.54 ± 1.22 *vs.* 2.46 ± 1.13; IC 95% 1.55–6.70; $p \leq 0.001$). *Conclusion*. A national strategy to facilitate access to care for patients living with sickle cell disease is imperative. Moreover, emphasis should be placed on the prevention and early management of acute complications of SCD.

1. Introduction

Sickle cell disease is a genetic disease of hemoglobin (Hb) that causes the synthesis of a modified Hb called Hb S. It is the world's most common hemoglobinopathy, especially in sub-Saharan Africa, where 85% of children affected by the disease are born [1, 2]. In the Congo, homozygous and heterozygous affect, respectively, 1.25% and 25% of the population [3]. In their deoxygenated form, Hb S molecules have the property of polymerizing to form intracellular crystals that deform the red blood cell (RBC), giving it its characteristic sickle shape. The deformed RBC thus loses its elasticity properties necessary to pass through the microcirculation. Stiffening and deformation of the RBC and increased blood viscosity explain the vasoocclusive complications of the disease. In addition, they are destroyed faster than normal RBCs, which further accounts for hemolytic anemia [4].

Chronic hemolysis predisposes sickle cell patients to the development of pigment lithiasis [5, 6]. Its frequency increases with age, up to a quarter [7] to a third [8] of children. In Jamaica, they are under 8 years of age in 12% of cases, and this proportion rises to 23% among 11- to 13-year-olds [9]. LB can appear early in very young children under the age of 5, sometimes as young as 2.5 [8, 10]. In Saudi Arabia, just over a third of the children involved are under the age of 12 (35.9% of cases), with a median diagnostic age of 6.9 ± 3.4 years [11]. In the Congo, LB is the most common chronic complication (40.31%) of sickle cell disease in adults [12]. These data on the child are rare. Moreover, cholecystectomy, known as "prophylactic" meaning performed before any complication, is not always accessible to families because of its cost. As a result, cholelithiasis can be an impediment to a child's quality of life through recurrent abdominal pain or even infections and can affect the prognosis due to complications such as computational migration through the bile duct main, cholecystitis, angiocholitis, or pancreatitis. Special emphasis should, therefore, be placed on its prevention or at least ways of delaying its occurrence. This work aimed to identify the factors associated with the occurrence of LB in young children in Brazzaville.

2. Materials and Methods

2.1. Study Settings and Design. This was a case-control study comparing sickle cell children under the age of 13. The first group consisted of children with symptomatic or no symptomatic cholelithiasis (cases). The second group consisted of children presenting no clinical signs suggestive of cholelithiasis and presenting a normal abdominal ultrasound at the time of inclusion in the study. The average age of diagnosis of biliary lithiasis frequently reported in the literature is 12. Thus, during our study, we selected children aged 12 and under to identify factors associated with the earlier onset of complications by studying the youngest subjects.

It was conducted over a period of 5 years and 6 months from January 2017 to June 2022. It was set up at the National Reference Center for Sickle Cell Disease "Antoinette Sassou N'guesso" in Brazzaville, which is the country's largest center dedicated to the management of people with the disease since 2017. Patients come from every department in the country. An abdominal ultrasound is prescribed as part of a systematic assessment from the age of 10 years or earlier if there are signs suggesting cholelithiasis. The cases were listed, and then each was matched to two controls based on age. Their data were collected retrospectively from medical records.

2.2. Study Variables. The variables studied were sociodemographic (socioeconomic status, diet), clinical (body mass index at diagnosis of cholelithiasis for cases and at inclusion for controls, the average annual frequency of vasoocclusive crisis and hospitalization for vasoocclusive crisis for 3 years before diagnosis of cholelithiasis for cases and 3 years prior to inclusion for controls, and number of blood transfusions since birth and whether or not there are other chronic complications at diagnosis of cholelithiasis for cases and at inclusion for controls), biological (type of sickle cell anemia, intercritical blood count including leukocyte count, Hb rate, mean globular volume, mean corpuscular concentration in Hb, and platelet count), and therapeutic (treatment with hydroxyurea prior to diagnosis of cholelithiasis for cases and prior to inclusion for controls and quality of systematic follow-up).

Drawing on the poverty index considered by the World Bank [13], we considered three socioeconomic statuses:

(i) Low: anyone in household living on less than $2.15 per day (1300 CFA)

(ii) Middle: anyone in household living on between $2.15 and $4.30 per day

(iii) High: anyone in household living on beyond $4.30 per day (2600 CFA)

We considered the diet to be

(i) high in fat when the patient consumed at least four times a week one of the following foods or groups of foods: beef/deli, fried foods, peanut (in all its forms), cheese/butter/milk, and legumes

(ii) low in fiber when the patient consumed less than four times a week one of the following foods or groups of foods: vegetables, fruits, and cereals

For blood count, the intercritic phase was defined by a period of at least 4 months characterized by the absence of acute infectious, vasoocclusive, and/or anemic complications. Anemia was considered moderate if Hb was above 6 g/dl and severe if it was below or equal to 6 g/dl. Systematic follow-up was considered regular when the child presented at least once a quarter to the National Reference Center for Sickle Cell Disease; it was considered irregular below 4 annual visits.

2.3. Statistical Analyses. SPSS version 25 was used for data analysis. The results of the qualitative variables are presented in absolute values and percentages; those of the quantitative variables are in the form of the mean (standard deviation), minimum, and maximum. The chi-squared statistical tests and the odds ratio were used for the comparison of variables, with a threshold of significance $p < 0.05$ and a 95% confidence interval. The univariate statistical analysis was conducted.

3. Results

During the study period, 101 children (aged 0–18 years) were diagnosed with cholelithiasis, 41 of whom were 12 years of age and younger. Thirty-seven complete files were used for this study. The average age of children was 9.70 ± 1.73 years with extremes of 6 and 12 years. The 10–12 age group was the most represented (22 cases or 59.45%) followed by 7–9 years (12 cases or 32.43%). Three children (8.10%) were 6 years old.

The circumstances for the discovery of cholelithiasis were isolated biliary colic (21 cases or 56.76%), followed by

cholecystitis (7 cases), systematic ultrasound (6 cases), angiocholitis (2 cases), and biliary peritonitis (1 case). The gallbladder was the primary site of the stones (32 cases *vs.* 5 cases in the main bile duct), and gallstones were most often multiple (86.49% of cases).

The sex ratio was 0.68 in the cases group *vs.* 1.38 in the controls group.

The average frequency of blood transfusions was 5.54 ± 1.22 in the cases group with extremes of 0 and 20. It was 2.46 ± 1.13 with extremes of 0 and 10 in the controls group.

The average vasoocclusive crisis (VOC) and hospitalization for VOC counts were 5.43 ± 1.32 (extremes 0 and 20) and 1.97 ± 0.60 (extremes 0 and 6) in the cases group *vs.* 5.39 ± 1.20 (extremes 0 and 10) and 1.58 ± 0.69 (extremes 1 and 5) in the controls group. A 12-year-old with cholelithiasis also had avascular osteonecrosis of the femoral head. No chronic complications were recorded in the controls.

Table 1 presents the sociodemographic and clinical characteristics of sickle cell children with and without cholelithiasis and their relationship to cholelithiasis at the National Reference Center for Sickle Cell Disease.

The majority of children with low socioeconomic status had a low-fiber diet (19/31) and irregular medical follow-up (17/31). Moreover, five of the six children with an average socioeconomic level had regular medical follow-ups.

Among children with cholelithiasis, 18 (48.65%) were transfused at least 5 times (including 6 children 10 or more times) *vs.* 10 (13.51%) in the controls group, including 1 child at least 10 times. Therapeutically, 12 children (32.43%) were taking hydroxyurea in the cases group *vs.* 25 (33.78%) in the control group. The average duration of treatment was 37 months for cases and 28 months for controls. The main indication was the high frequency of VOC followed by priapism in boys.

Genotype SS was most represented (83.78% *vs.* 71.62%), followed by sickle beta-zero-thalassemia (13.51% *vs.* 10.81%) and sickle beta-plus-thalassemia (2.70% *vs.* 17.57%). All children had moderate anemia. For cases, the mean Hb rate was 6.17 ± 0.44 g/dl *vs.* 6.67 ± 0.27 g/dl for controls.

The average MCV was 76.46 ± 2.14 for cases *vs.* $65.53\pm$ for controls.

The average MCHC was 21.42 g/dL for cases *vs.* 28.11 g/dL for controls.

Table 2 shows the type of SCD and baseline biological parameters in sickle cell children with and without cholelithiasis and their relationship to cholelithiasis at the National Reference Center for Sickle Cell Disease.

The average number of platelets was 302 ± 30 for cases *vs.* 327 ± 20 for controls. The average number of WBC was 11499 ± 11 for cases *vs.* 12756 ± 23 for controls.

4. Discussion

A very significant strong link has been established between the low socioeconomic status and the occurrence of cholelithiasis. In addition, the majority of children with low socioeconomic status had a low-fiber diet and irregular medical follow-up. These results illustrate the likely link between the socioeconomic level, the type of diet, and the quality of monitoring. The irregularity in the rhythm of routine checks was established as a factor significantly associated with the occurrence of cholelithiasis. This could be the expression of the indirect link between poor adherence to treatment and thus poor preventive and curative management of acute complications of the disease, especially those causing hyperhemolysis. Indeed, in our series, patients who have been transfused more than three times since birth were 3 times more likely to develop cholelithiasis. The same observation was made by Koueta in Burkina Faso [14]. In the USA, a study on the effects of chronic transfusions on abdominal sonographic abnormalities in children with sickle cell anemia reported that gallbladder disease was correlated with older age ($p = 0.002$), longer duration of transfusions ($p = 0.034$), and higher total bilirubin ($p \leq 0.001$) [15].

Transfusions performed in children at the National Reference Center for Sickle Cell Disease are mainly punctual and carried out for hyperhaemolytic crises, of which bacterial infections and malaria are the main causes. In this context, patients are generally admitted for clinical signs of severe anemia. More rarely, it is about systematic transfusions performed for the management of chronic complications of sickle cell disease such as stroke, but chronic transfusions are difficult to achieve because of the availability of blood products and their cost. The high incidence and severity of bacterial infections justify prevention efforts through antibiotic prophylaxis and vaccination. Moreover, in areas of high malaria prevalence, special emphasis should be placed on mechanical prevention, including insecticide-treated nets and environmental sanitation.

No significant association was found between VOC frequency and the occurrence of LB. Koueta reported a significant risk (OR = 7.6) when children had at least three VOCs per year [14]. Alhawsawi in Saudi Arabia and Martins in Brazil reported similar results to ours with a higher prevalence of LB in children of phenotype SS compared to Sβ-thalassemias and SC without the difference being significant [11, 16].

In the Adeniyi study in Nigeria, the prevalence of gallstones increased with an increase in the number of crisis in the children, but this was not statistically significant [17]. In France, Kamdem reported that among clinical events, VOC, acute chest syndrome, and febrile episodes significantly increased the risk ($p \leq 0.001$) [18]. In the literature, VOC frequency is rather a known predictor of ischemic complications, including the avascular osteonecrosis of the femoral head [19].

Da Silva in Portugal identified a statistically significant association between a higher number of hospitalizations ($p \leq 0.001$), chronic complications of the disease ($p = 0.035$), and leukocytes >15 000/μL [20].

In a French study, among the baseline biological parameters, hemoglobin, WBC, neutrophils, platelets, MCV, and bilirubin were not significant factors whereas HbF level

Table 1: Sociodemographic and clinical characteristics of sickle cell children with and without cholelithiasis and their relationship to cholelithiasis at the National Reference Center for Sickle Cell Disease.

Characteristics	Cholelithiasis		Without cholelithiasis		OR	IC 95%	*P*
	n	(%)	*n*	(%)			
Gender							
Female	22	59.4	31	41.9			
Male	15	40.6	43	58.1			
Socioeconomic status							
Low	31	83.78	34	45.95	2.38	1.46–3.89	**≤0.001**
Middle	6	16.22	40	54.05	0.07	0.01–0.52	
High	0	—	0	—			
Diet							
High in fat	3	8.11	0	0	0.9	0.79–1.03	0.12
Low in fiber	23	62.16	11	14.86	6.82	0.71–27.18	**≤0.001**
Body mass index							
Normal	28	75.68	42	56.76			
Underweight	6	12.22	17	22.97	0.99	0.83–1.97	
Overweight	0	0.00	1	1.35	1.14	0.17–7.40	0.89
Annual frequency of VOC* in the last 3 years							
Mean (min-max)	5.43 ± 1.32 (0–20)		5.39 ± 1.20 (0–10)				
0–3	15	40.54	20	27.03	0.85	0.60–1.20	0.35
4 and more	22	59.46	54	72.97	1.59	0.58–4.30	
Annual frequency of hospitalization for VOC* in the last 3 years							
Mean (min-max)	1.97 ± 0.60 (0–6)		1.58 ± 0.69 (1–5)				
0–3	30	81.08	64	86.49	0.99	0.88–1.12	0.92
4 and more	7	18.92	10	13.51	1.14	0.08–17.11	
Number of blood transfusion since birth							
Mean (min-max)	5.54 ± 1.22 (0–20)		2.46 ± 1.13 (0–10)				
0–3	13	35.14	57	77.03	0.3	0.13–0.67	**≤0.001**
4 and more	24	64.86	17	22.97	3.22	1.55–6.70	
Hydroxyurea treatment							
Yes	12	32.43	25	33.78	1.14	0.51–2.52	0.75
No	25	67.57	49	66.22			
Quality of systematic follow-up							
Regular	19	51.35	59	79.73	0.54	0.33–0.88	
Irregular	18	48.65	15	20.27	3.41	1.28–9.04	**0.005**

*Vasoocclusive crises (pain crises).

($p = 0.028$), reticulocyte count ($p \leq 0.001$), and LDH ($p = 0.020$) significantly increased the risk for gallstones. The multivariate Cox analysis including all the significant risk factors in the univariate analysis retained the deletion of 2 alpha genes (HR = 4.66; 95% CI: 1.11–19.52; $p = 0.035$) which decreases the risk, the presence of at least one allele (TA_8) (HR = 2.26 : 95% CI: 1.07–4.78, $p = 0.032$), which increases the risk, and the baseline reticulocytes count per 1×10^9/L increase (HR: 1.001; 1.000–1.002, $p = 0.005$), as independent and significant predictive factors for gallstones [18]. Meta-analysis including 34 studies showed that the risk of developing cholelithiasis was significantly associated with lower total hemoglobin level ($p = 0.002$), lower hemoglobin F level ($p = 0.003$), higher total serum bilirubin level ($p \leq 0.001$), higher reticulocytes count ($p = 0.007$), and UDP-glucuronosyltransferase-1A1 enzyme (UGT1A1) promoter polymorphism [21]. The Olatunya study in Nigeria highlights the contribution of UGT1A1 polymorphisms, a nonglobin genetic factor, to the laboratory and clinical manifestations of young Nigerian SCA patients for the first time. It also shows that children with coinheritance of low UGT1A1 (TA) n affinity genotypes may be at risk of gallstone [22].

There were no significant differences between the Hb SS and Hb S/β thalassemia groups. Alhawsawi in Saudi Arabia and Martins in Brazil reported similar results to ours with a higher prevalence of cholelithiasis in children of genotype SS compared to Sβ-thalassemias and SC without the difference being significant [11, 16].

The use of hydroxyurea was not significantly related to the occurrence of cholelithiasis. Martins reported the same [16].

Table 2: Type of SCD and baseline biological parameters in sickle cell children with and without cholelithiasis and their relationship to cholelithiasis at the National Reference Center for Sickle Cell Disease.

Characteristics	Cholelithiasis		Without cholelithiasis		OR	IC 95%	*P*
	n	(%)	*n*	(%)			
Type of SCD							
S/β thalassemia*	6	16.22	21	28.38	0.57	0.25–1.29	0.16
SS	31	83.78	53	71.62	1.17	0.96–1.43	
SC	0	—	0	—			
Hb (g/dL)							
<6	13	35.14	14	18.92	1.82	0.69–4.74	0.21
≥6	24	64.86	60	81.08	0.8	0.54–1.15	
MCV** (FL)							
<100	24	64.86	44	59.46	0.86	0.80–1.47	0.58
≥100	13	35.14	30	40.54	1.09	0.44–1.62	
MCHC*** (g/dL)							
<32	19	51.35	23	31.08	1.26	0.63–2.52	0.81
≥32	18	48.65	51	68.92	0.85	0.53–1.38	
WBC**** (/mm^3)							
<12000	21	56.76	44	59.46	0.67	0.39–1.13	0.11
≥12000	16	43.24	30	40.54	1.7	0.85–3.38	
Platelets (giga/L)							
150–450	31	83.78	56	75.68	1.28	0.89–1.82	0.17
≥450	6	16.22	18	24.32	0.51	0.18–1.41	

*Sickle beta-zero-thalassemia (5 cases vs 8 controls) and sickle beta-plus-thalassemia (1 case vs 13 controls). **Mean corpuscular volume. ***Mean corpuscular Hb concentration. ****White blood cells.

5. Conclusion

A relationship was found between a low socioeconomic status, a low-fiber diet, and a higher number of blood transfusions. A national strategy to facilitate access to care for people living with sickle cell disease is imperative. In addition, in our context, where acute hemolytic anemia is primarily caused by malaria and bacterial infections, emphasis must be placed on the prevention and early management of infections.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest concerning this article.

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Research Article

Preterm Delivery and Neonatal Deaths among Anaemic Pregnant Women in the Bolgatanga Metropolis of Ghana

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Preterm deliveries and neonatal deaths as functions of anaemia in pregnancy are of major public health interest. However, data on the prevalence of preterm deliveries and their association with mortality in anaemic pregnant women in the study area are scanty. Thus, the study sought to investigate the prevalence of preterm delivery and neonatal deaths among anaemic pregnant women in the Bolgatanga Regional Hospital in the Upper East Region of Ghana during the past five years. A retrospective study design was adopted, and data were gathered between March and May 2016. Records of women who were anaemic during any trimester of their pregnancy and delivered in the hospital within the last five years were included in the study. In all, two hundred (200) cases were reviewed. Data on the sociodemographic characteristics, health status, and birth outcome of participants were captured, and analyses were conducted using SPSS version 21 while considering significant differences at $p < 0.05$. The study revealed that more than half of the anaemic women (52.5%, $n = 105$) had preterm deliveries, while neonatal mortality was 8.5% ($n = 17$). The proportion of mothers who received dietary or medical intervention for the treatment of anaemia and the number of attendances to antenatal clinics were comparable between preterm and normal-term mothers ($p > 0.05$). Mothers with preterm deliveries had a higher risk of neonatal mortality (AOR = 13.66, 95% CI = 1.65–113.30, and $p = 0.015$). This study has shown that anaemia in pregnancy increases the risk of preterm delivery and neonatal death. It is recommended that extra care be given to pregnant women with anaemia, while further studies are conducted with a larger sample size to substantiate the claims made in this study.

1. Background

Anaemia has remained a major public health concern in low and middle-income and high-income countries [1]. Globally, anaemia affects 1.62 billion people, which corresponds to 24.8% of the world's population [2], and vulnerable groups such as school-age children and pregnant women suffer the most from its consequences [2]. Among pregnant women, anaemia prevalence is reported to be very high globally, with about 40% being affected [3]. Poor birth outcomes such as stillbirth, preterm delivery, and low birth weight (LBW) are associated with anaemia and thus call for special attention [4]. In view of this, routine haemoglobin (Hb) assessments for pregnant women are performed during their visit for antenatal care (ANC) to monitor and manage anaemic conditions. As a routine, haematinics are given to these pregnant women, which have been shown to improve their anaemic situation [5].

Several factors are known to be associated with anaemia in pregnant women. These range from parasitic infections (helminths and malaria) [6], haemoglobinopathy [7], late initiation of ANC [8], poor diet and gestational age at first ANC [9], and low ANC visits (less than 4) [10] among others.

The World Bank report has indicated a gradual fall in the anaemia prevalence among Ghanaian pregnant women, from 59% in 1990 to 53% in 2016 [11]. According to regions, there were substantial disparities, ranging from a prevalence

of 61% in the Greater Accra Region to 83% in the Northern Region [12]. However, data on the prevalence of preterm delivery and neonatal mortality among anaemic pregnant women in the study area are scanty. Thus, the aim of the study was to determine the prevalence of preterm deliveries and neonatal deaths among anaemic pregnant women in the Bolgatanga Regional Hospital in the Upper East Region of Ghana.

2. Methodology

2.1. Study Design and Study Area. A retrospective cross-sectional study design was carried out in March and April 2016 in the Bolgatanga Regional Hospital where most of the people in the region seek health care. Bolgatanga Regional Hospital is located in the Bolgatanga municipal of Ghana (Figure 1 as BRH) and serves the entire Upper East Region as well as some residents of the Upper West Region. Subjects were recruited based on the fact that they were anaemic during any period of their pregnancy. The gestational weeks of their children were considered to identify those who gave birth preterm (before the required 9 months) or normal term.

2.2. Sample Siz. With a prevalence of 53% of anaemia among Ghanaian pregnant women according to the World Bank Report [11], the Cochrane sample size formula [14] was used to estimate the minimum sample size for the study:

$$\begin{aligned} \textbf{sample size } (\mathbf{n_o}) &= \left(\frac{\text{z2pq}}{\text{e2}}\right), \\ &\text{where,} \\ z &= 1.96, \\ p &= 0.530, \\ q &= 1 - 0.530 \\ &= 0.467, \\ e &= 0.05, \end{aligned} \tag{1}$$

where z = confidence interval; e = margin of error; n_o = sample size; and p = prevalence of anaemia of the study population at 53.0%, i.e., 0.530:

$$\begin{aligned} (\mathbf{n_o}) &= \frac{1.96\,\text{x}1.96\ (0.530)\,(1 - 0.530))}{0.05\,\text{x}\,0.05}, \\ (\mathbf{n_o}) &= \frac{3.8416\ (0.2475)}{0.0025}, \\ \textbf{sample size } (\mathbf{n_o}) &= 380. \end{aligned} \tag{2}$$

Adding an attrition of 5% of the total sample size (380), which is 19 rounded to the nearest decimal, finally gave a total sample size of 399.

2.3. Study Population and Data Extraction. Anaemic pregnant women (Hb < 11 g/dL) comprised the study population. Data from the health records of these anaemic pregnant women and their delivery outcomes for the last five years (from 2011 to 2016) were extracted. The study subjects were further divided into preterm (those who delivered their babies before 37 weeks), and the rest were normal terms. In these two groups (preterm and normal term), the prevalence of mortality was determined. Maternal mortality was not considered in the recruitment criteria and thus was not included in the data for analysis.

2.4. Data Handling and Analysis. The data extracted were double entered to minimize data entry errors. Cleaning and coding were conducted before analysis. The data were analyzed using Microsoft Excel 2013 and Statistical Package for Social Sciences (SPSS) version 21 (IBM, Chicago Illinois, USA). The result was then presented in frequency, cross-tabulations, and diagrams as necessary, while $p < 0.05$ was set for statistical significance. Predictors of preterm delivery were evaluated by multinomial logistic regression analyses.

2.5. Ethical Consideration. To adhere to the highest ethical conduct of the study, serious consideration was made regarding study approval and participant consent to be part of the study. To this end, ethical clearance was sought from the joint School of Medicine and Health Sciences/School of Allied Health Sciences with SMSAHS/JIRB/0015 as the number. Permission was sought from the administrator and the head of the Gynaecology Unit of the BRH.

3. Results

3.1. Distribution of Sociodemographic Information among Mothers. A majority (55.5%, $n = 111$) of the mothers were aged between 21 and 30 years (Table 1). Majority (84.5.0%, $n = 169$) were employed, of which most (38.0%, $n = 76$) were artisans. Close to 64.0% ($n = 128$) were married, while the remaining unmarried mothers were either single, divorced, separated, or widows. A larger proportion (87.5%, $n = 175$) of the mothers had attained some level of formal education, of which the majority (68.5%, $n = 137$) had attained basic education (primary and junior high school (JHS)) (Table 1). It was realized that the recruited sample size was lower than the calculated sample size. This may be attributed to the inability to access data dating more than 5 years.

3.2. Clinical and Obstetric Characteristics of the Mothers. Anaemia was diagnosed by maternal haemoglobin levels of 11 g/dL [11]. The majority of mothers (73.6%, $n = 148$) had between 4 and 6 antenatal clinics (Table 2). Based on the clinical history and source of anaemia, dietary (76.5%, $n = 153$) or medical (23.5%, $n = 47$) interventions were prescribed for the mothers during their antenatal visit prior to delivery (Table 2). More than half of the mothers (52.0%,

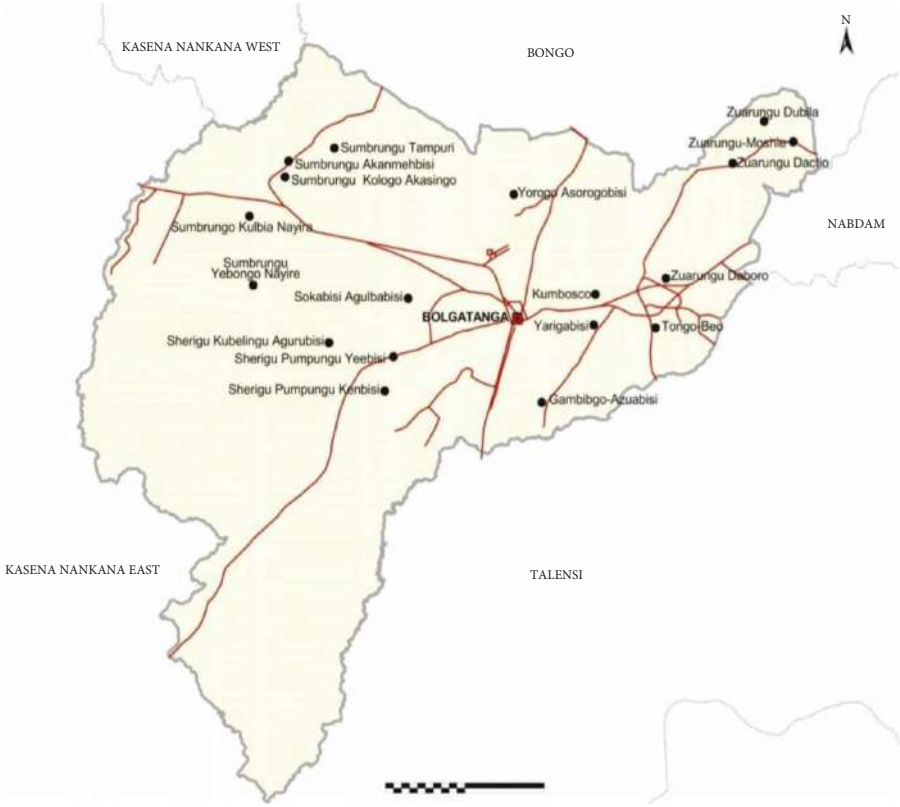

Figure 1: Map of Bolgatanga municipal [13].

Table 1: Sociodemographic characteristics of the study participants ($n = 200$)[#].

Category	Subcategory	*n* (%)	95% CI
Age	11–20	50 (25.0)	40, 64
	21–30	111 (55.5)	97, 125
	31–40	29 (14.5)	20, 40
	41–50	10 (5.0)	5, 17
Occupational status	Artisan	76 (38.0)	63, 90
	Trader	52 (26.0)	41, 65
	Farmer	26 (13.0)	18, 36
	Civil servant	9 (4.5)	4, 16
	Other*	6 (3.0)	3, 12
	Unemployed**	31 (15.5)	22, 42
Marital status	Married	128 (64.0)	114, 141
	Single	48 (24.0)	37, 61
	Divorced	8 (4.0)	4, 15
	Separated	1 (0.5)	0, 5
	Widow	15 (7.5)	9, 24
Formal education	None	25 (12.5)	17, 35
	Primary	43 (21.5)	32, 55
	J.H.S	94 (47.0)	80, 108
	S.H.S	22 (11.0)	14, 32
	Vocational/technical	8 (4.0)	4, 15
	Tertiary	8 (4.0)	4, 15

n (%): number and proportion; *hairdressers and seamstress; **housewife; [#]recruited study subjects were lower than the estimated sample size. (95% CI): 95% confidence interval; S.H.S: senior high school.

$n = 104$) had preterm delivery as they gave birth before 37 weeks of gestation (Table 2). Neonate mortality was observed in 8.0% ($n = 16$) of the mothers (Table 2).

3.3. Comparison of Socioeconomic, Clinical, and Obstetric Outcomes between Mothers with Preterm and Normal Delivery. No age differences were observed between

Table 2: Clinical and obstetric information of the study participants ($n = 200$).

Category	Subcategory	n (%)	95% CI
Intervention when the mother was diagnosed anaemic	Dietary	153 (76.5)	141, 164
	Medical	47 (23.5)	36, 59
Number of antenatal visits	1–3	28 (14.0)	19, 39
	4–6	147 (73.5)	134, 158
	7–9	25 (12.5)	17, 35
Number of weeks the child was conceived before birth	Before 37 weeks	104 (52.0)	90, 118
	37 weeks and above	96 (48.0)	82, 110
Preterm or normal term	Normal term	96 (48.0)	82, 110
	Preterm	104 (52.0)	90, 118
Neonate mortality	Yes	16 (8.0)	10, 25
	No	184 (92.0)	175, 190

n (%): number and proportions; (95% CI): 95% confidence interval.

preterm and normal-term mothers ($X^2 = 3.84$ and $p = 0.281$), Table 3. Similarly, no differences in occupational ($X^2 = 2.30$ and $p = 0.129$), marital ($X^2 = 0.39$ and $p = 0556$), and educational ($X^2 = 0.18$ and $p = 0.669$) statuses existed between preterm and normal-term mothers. The proportion of mothers who had received dietary or medical intervention for the treatment of anaemia was observed to be similar for both preterm and normal-term mothers ($X^2 = 0.73$ and $p = 0.393$). Moreover, the number of attendances to antenatal clinics did not differ between these mothers ($X^2 = 4.32$ and $p = 0.157$). However, the proportion of preterm women with neonatal mortality was higher than that of normal-term women ($X^2 = 12.16$, $p < 0.001$), Table 3.

3.4. Factors That Predict Preterm Delivery among Mothers. The contributions of socioeconomic, clinical, and obstetric variables as predictors of preterm delivery were evaluated by multinomial logistic regression analyses. Before the analyses, multicollinearity issues among the predictor variables were resolved by a linear regression model, and predictors with a variance of inflation (VIF) of <2.000 were included in the multinomial regression model. In addition, Pearson correlation analyses were run to ensure there were no significant correlations among the predictor variables. The multinomial analyses showed that age, occupational, marital, and educational statuses did not influence the occurrence of preterm delivery (Table 4). Moreover, the number of antenatal clinics attended or the type of intervention used as a remedy for maternal anaemia did not influence the occurrence of preterm delivery (Table 4). However, mothers with preterm delivery had a higher risk of child mortality (AOR = 13.66, 95% CI = 1.65–113.30, and $p = 0.015$, Table 4).

4. Discussion

Anaemia in pregnancy is of major public health concern, which calls for a pragmatic approach, but relevant data are lacking in the current study setting. The current study has shown that anaemia in pregnancy increases the risk of preterm delivery and neonatal death. Furthermore, preterm neonates are more likely to die within the first few days of birth.

Several factors have been associated with anaemia in pregnancy, including infectious diseases (malaria, helminths, hepatitis B, and HIV), low level of education, gestational age at the first ANC visit, and consumption of fish and snails [9, 15]. Meanwhile, preterm delivery and significant neonatal mortality were associated with anaemia in the current study; thus, anaemia in pregnancy has a great impact on birth outcomes.

The high risk of neonatal death in anaemic pregnant women may be attributed to multiple factors. One of them is the fact that anaemia in pregnancy results in low tolerance to loss of blood leading to impaired function and cardiac failure [16]. Related to this is iron deficiency, which increases oxidative damage to erythrocytes and the fetoplacental unit [17]. This deficiency in iron increases the risk of maternal infections. This further stimulates corticotropin-releasing hormone (CRH) production, making it a high-risk factor for preterm delivery on the basis that higher concentrations of CRH during labour also predict a shorter labour duration [18–20]. While high CRH is implicated in preterm delivery, it is important to state here that normal CRH concentration does not indicate that a normal delivery date is assured; this is because infections affecting the foetus and other problems can result in preterm delivery irrespective of the CRH level. Furthermore, there was a considerable difference in individual normal CRH concentrations. Nevertheless, the concentrations of CRH can significantly predict the duration of gestation. Meanwhile, it is observed that in humans, hypoxia, stress, preeclampsia, eclampsia, and inflammatory cytokines lead to increased placental CRH secretion [17].

With the relatively high preterm deliveries and neonatal deaths observed in the current study, it is important that interventions such as free distribution of insecticide-treated nets (ITNs) [21, 22], early initiation and improved antenatal care (ANC) [23], regular iron supplementation, screening of genetic diseases (e.g., G6PDd), and treatment of infectious diseases [24] be enhanced with focused and targeted education. The expectation is that, with such urgency and importance attached to these interventions, the level of anaemia in pregnancy will reduce significantly and consequently lower preterm delivery as well as neonatal deaths.

Table 3: Differences in socioeconomic and obstetric characteristics among mothers with preterm and normal-term delivery ($n = 200$).

Category	Subcategory	Normal delivery	Preterm delivery	(X^2), *p
Socioeconomic variables, n (%)				
Age	11–20	22 (44.0)	28 (56.0)	3.84, 0.281
	21–30	58 (52.3)	53 (47.7)	
	31–40	10 (34.5)	19 (65.5)	
	41–50	6 (60.0)	4 (40.0)	
Occupational status	Unemployed	11 (35.5)	20 (64.5)	2.30, 0.129
	Employed	85 (50.3)	84 (49.7)	
Marital status	No	37 (51.4)	35 (48.6)	0.39, 0.556
	Yes	59 (46.1)	69 (53.9)	
Formal education	No	13 (52.0)	12 (48.0)	0.18, 0.669
	Yes	83 (47.4)	92 (52.6)	
Clinical and obstetric outcomes, n (%)				
Intervention for anaemia	Medical	20 (42.6)	27 (57.4)	0.73, 0.393
	Dietary	76 (49.7)	77 (50.3)	
Number of antenatal visits	1–3	9 (32.1)	19 (67.98)	4.32, 0.115
	4–6	72 (49.0)	75 (51.0)	
	7–9	15 (60.0)	10 (40.0)	
Neonate mortality	No	95 (51.6)	89 (48.4)	**12.16, <0.001**
	Yes	1 (6.3)	15 (93.8)	

n (%): number and proportions. *Analyzed using Pearson's chi-square test or Fisher's exact test. χ^2 = Pearson's chi-square value. p significant at <0.05 (2-tailed). For formal education, yes: primary, JHS, SHS, vocational/technical, and tertiary, while no: none. For occupational status, employed: artisans, traders, farmers, civil servants, and others (hairdressers and seamstresses), while unemployed: housewife. For marital status, yes: married, while no: single, divorced, separated, and widow.The significance of the bold values is that the association is significant.

Table 4: Factors that predict preterm delivery among study participants.

Parameters		B	Standard error	Exp (B)/AOR	95% CI AOR	p
Age	11–20	−0.287	0.802	0.75	0.16, 3.62	0.721
	21–30	−0.236	0.736	0.79	0.19, 3.34	0.749
	31–40	0.666	0.793	1.95	0.41, 9.21	0.401
	41–50	0[b]	—	—	—	—
Occupational status	Unemployed	0.851	0.560	2.34	0.78, 7.02	0.129
	Employed	0[b]	—	—	—	—
Marital status	Not married	−0.449	0.360	0.64	0.32, 1.29	0.212
	Married	0[b]	—	—	—	—
Educational status	None	−0.329	0.488	0.72	0.28, 1.87	0.499
	Formal education	0[b]	—	—	—	—
Intervention for maternal anaemia	Medical	0.127	0.385	1.14	0.53, 2.42	0.742
	Dietary	0[b]	—	—	—	—
Number of antenatal visits	1–3	0.820	0.626	2.27	0.67, 7.75	0.190
	4–6	0.444	0.468	1.56	0.62, 3.89	0.343
	7–9	0[b]	—	—	—	—
Neonate mortality	Yes	2.614	1.079	13.66	1.65, 113.30	0.015

p: analyzed by multinomial logistic regression analyses and considered significant at < 0.05 (2-tailed). The reference category is normal-term delivery. b: parameter considered redundant and set to zero. B: regression coefficient. ExpB: exponentiation of B, which is the same as AOR: adjusted odds ratio. 95% CI: 95% confidence interval.

The current study has shown that the utilization of healthcare assessment was very beneficial to anaemic pregnant women. For example, women who attended the higher number of antenatal services recorded the least number of preterm births compared to those who did not attend antenatal frequently, while anaemic pregnant women who did not attend antenatal services frequently were more likely to give preterm babies. Furthermore, interventions that were initiated with anaemic pregnant women were also crucial in ensuring that the baby was born alive. Dietary and medical care given to these anaemic pregnant women improved the survival of the babies. It is at these ANC visits that pregnant women are educated and given targeted interventions after being screened. Thus, antenatal visits should be encouraged and promoted. Further studies are needed on a larger sample size to explore the extent to which

parasitic infections [25], haemoglobinopathies [7], late initiation of ANC [8], and poor diet and gestational age [9] affect pregnancy outcomes.

The youthful age of the study population is encouraging, and the fact that most are employed and had some form of formal education as reported in another study [15] suggests that they are capable of managing their homes and can afford to get the necessary food items to improve their haemoglobin level. However, the majority of the study subjects (>60%), who are traders and artisans are noted to be busy and close late at night from their trading activities [26], are unable to attend their antenatal care services regularly and are not available at home for home health service delivery which is organized for pregnant women and young children on Thursdays and Fridays in the study area.

4.1. Limitations. A few limitations were observed in the current study. One of them is the fact that we were unable to get the required number for the study. This may influence the outcome of the findings and conclusions. Retrospective studies also have a deficiency of not getting certain clarifications one will want to get in the data captured, which the responses from the other study subject recruited at the time of the study could not address. Furthermore, anaemia may not be the only factor in determining neonatal death, although it may be strongly associated [27].

5. Conclusions and Recommendations

In conclusion, anaemia in pregnancy increases the risk of preterm delivery and neonatal death. Therefore, extra care should be given to pregnant women with anaemia, while further studies are conducted with a larger sample size to substantiate the claims made in this study.

Data Availability

Data can be made available upon reasonable request from the corresponding author.

Disclosure

This work was presented during the Keystone Conference that was scheduled for October 21–23, 2020, with the conference theme "Optimizing Nutrition for Maternal, Newborn, and Child Health" in the eKeystone Symposium [28]. This study was carried out as part of the research activities of the university.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

GKH conceived the idea and supervised the study. GKH, PAA, and BSM performed the data analysis and drafting of the manuscript. All the authors reviewed the manuscript for intellectual content.

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Research Article

Red Blood Cell Alloimmunization and Autoimmunization in Blood Transfusion-Dependent Sickle Cell Disease and β-Thalassemia Patients in Al-Ahsa Region, Saudi Arabia

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Introduction. The risk of developing transfusion-related complications, especially alloimmunization, is an ongoing concern for transfusion-dependent patients. It is important to determine the rate of alloimmunization and autoimmunization in Al-Ahsa Region, Saudi Arabia, where sickle cell disease (SCD) and thalassemia incidence rates are the highest in Saudi Arabia. *Methods*. A cross-sectional study was conducted to review the transfusion history of patients with SCD and thalassemia at the King Fahad Hospital (KFH) in Al-Ahsa, Saudi Arabia. 364 transfusion-dependent patients were included in this study. *Results*. Alloimmunization rates in patients with SCD and thalassemia were 16.7% and 11.97%, respectively, while autoimmunization rates in patients with SCD and thalassemia were 5.3% and 0.7%, respectively. The most frequent alloantibodies among the study participants were against Kell, Rh blood group systems. *Conclusion*. Blood transfusion-related alloimmunization and autoimmunization compromise the proper management of chronically transfused patients. Ideally, extended matched phenotyping should be implemented to prevent alloimmunization and reduce the risk of developing blood transfusion-related alloantibodies.

1. Introduction

Prior to the discovery of the ABO blood groups by Karl Landsteiner in 1901, all blood was considered the same leading to critical blood transfusion side effects [1, 2]. These side effects were due to incompatibilities in ABO blood type between donors and recipients, but since 1901, transfusions became more safe as harmful incompatibilities were reduced. In transfusion medicine today, ABO blood group antigens remain critically important as they are the most immunogenic of all the blood group antigens [3]. One of the most common causes of morbidity in blood transfusion is blood type incompatibilities due to clerical error [1, 2]. Incompatible blood group antigens can induce immune reactions, known as alloimmunization, in patients who lack the corresponding antigens on their red blood cells (RBCs). Aside from the transfusion of antigen positive blood into antigen negative patients, alloimmunization can also occur during pregnancy [4]. In addition to alloimmunization, transfusions can also induce autoimmunization where transfusion-related autoantibodies are hypothesized to develop against the patient's own cells.

Sickle cell disease and β-thalassemia are common hemoglobinopathies in Saudi Arabia. According to

a systematic review and meta-analysis of 18 studies, the prevalence of sickle cell disease in Saudi Arabia ranges from 0.9% to 4.2%, with the highest prevalence observed in the eastern and southern regions of the country [5]. β-thalassemia is also highly prevalent in Saudi Arabia, with a carrier rate of 3-4% in the general population [6]. In some areas, such as the Eastern Province, the prevalence of β-thalassemia is estimated to be as high as 15–20% [6].

Transfusion of RBCs is one of the most commonly used medical interventions in clinical settings accounting for more than 108 million units administered worldwide every year [7]. The major complication of regular blood transfusions, particularly in patients who are chronically transfused, is RBC alloimmunization [7]. Even though RBC alloimmunization mitigation strategies are implemented for chronically transfused patients, multitransfused patients are still at risk of developing alloantibodies [8]. Donor and recipient factors play a role in RBC alloimmunization. These factors range from characteristics of a particular blood group antigen to the recipient's ability to present the antigens to their immune system [9]. In addition to genetic factors, emerging data have highlighted the importance of environmental factors in the formation of RBC alloantibodies [10].

Recent studies investigating the prevalence and frequency of RBC antigens that cause hemolytic transfusion reactions in Saudi Arabia have focused on populations from Southwestern Saudi Arabia [11–13]. It is important to phenotype other populations in Saudi Arabia, particularly people from the Al-Ahsa Region where sickle cell disease (SCD) and β-thalassemia are endemic. These populations require regular blood transfusions to maintain healthy hemoglobin levels to improve oxygen-carrying capacity of blood and reduce the serious disease-associated complications [14, 15]. However, the development of alloantibodies associated with blood transfusions can negatively impact the health of these patients and complicate transfusion therapy [10]. This study was designed to identify the most common phenotypes associated with transfusion side effects among blood transfusion-dependent SCD and β-thalassemia patients from Al-Ahsa Region. Understanding these phenotypes will help lower the incidence of adverse transfusion outcomes by using extended phenotype matching to identify more compatible blood.

2. Subjects and Methods

2.1. Patients. This cross-sectional study was conducted in accordance with the code of conduct of research in Saudi Arabia and the 1964 Helsinki Declaration and its later amendments. This study was approved by the Research Ethical Committee of the Institutional Review Board of King Fahad Hospital in Al-Ahsa, Ministry of Health, Kingdom of Saudi Arabia (No. 33-EP-2022). The study was conducted over 5 months between May 2022 and October 2022 and included 362 patients, 284 transfusion-dependent β-thalassemia patients and 78 SCD patients. All patients received leukoreduced RBC transfusions.

Clinical and transfusion records of all patients were reviewed for demographic and clinical data including age, gender, age of initial transfusion therapy, transfusion frequency, total number of blood units transfused, and status of splenectomy. All data were collected with sociodemographic characteristics of participants included in Table 1.

2.2. Inclusion Criteria. Regardless of sex and age, only Saudi patients hospitalized for blood transfusions were included in this study.

2.3. Exclusion Criteria. Patients with a history of hematological malignancies were excluded from this study.

2.4. Transfusion Protocol. Transfusion policy adhered to international guidelines, including those established by the American Association of Blood Banks (AABB) and the Saudi Ministry of Health. To ensure the safety and efficacy of the transfusion process, a comprehensive screening was conducted to determine the presence of various blood group antigens, including A, B, O, AB, D, C, c, E, e, and K. The ID system gel cards (Bio-Rad, Dreieich, Germany) were utilized for antigen testing, while DiaClon ABO/D + reverse grouping and DiaClon Rh subgroups + K gel cards (Bio-Rad, Dreieich, Germany) were used for blood grouping and subtyping. Antibody screening and identification were also performed to detect the presence of any alloantibodies that may react with the donor's blood. Also, each sample underwent a direct antiglobulin test with a polyspecific anti-human globulin reagent (anti-IgG and anti-C3d) using the gel technique with a LISS/Coombs card (DiaMed GmbH, Switzerland), according to the method of Obaid et al. [16].

2.5. Statistical Analysis. A nonprobability sampling technique was utilized in this study. Sample size was calculated using a 95% confidence interval and 5% margin of error to include 385 participants. Frequencies of phenotypes in the Al-Ahsa population were compared with phenotype frequencies in other ethnicities by performing a chi-squared test. P values <0.05 and <0.01 indicated significant and highly significant differences, respectively.

3. Results

The rates of β-thalassemia and SCD alloimmunization in the 362 transfusion-dependent participants sampled in this study are presented in Table 2. Of the 362 transfusion-dependent participants, 284 (78.5%) were transfusion-dependent β-thalassemia patients and 78 (21.5%) were SCD patients. Of the β-thalassemia patients, 34 (11.8%) developed alloantibodies including 12 males (35%) and 22 females (65%). Of the SCD patients, 13 (16.7%) developed alloantibodies including 7 males (53.8%) and 6 females (46.2%). Among the 362 patients studied, 6 patients (1.7%) had positive direct antibody test (DAT) or autocontrol results including 2 β-thalassemia patients (33%) and 6 SCD

Table 1: Sociodemographic characteristics of β-thalassemia and sickle cell disease patients in Al-Ahsa Region, Saudi Arabia.

	β-thalassemia		Sickle cell disease	
	Number	%	Number	%
Sex				
M	12	35	7	53.8
F	22	65	6	46.2
Age				
<17	4	12	2	17
17–24	9	26	3	17
25–45	20	59	7	50
46–60	1	3	1	17
>60	0	0	0	0
Total	34	11.97	13	16.7

Table 2: Rates of β-thalassemia and sickle cell disease alloimmunization in Al-Ahsa Region, Saudi Arabia.

	Current study	Jazan [17]	Jeddah [18, 19]	[20] Eastern
β-thalassemia alloimmunization (n)	34 out of 284	7 out of 53	27 out of 134	N/A
Percentage (%)	11.8%	13.21%	20.15%	N/A
P value		0.0010	0.0001	
Sickle cell alloimmunization (n)	13 out of 78	50 out of 385	30 out of 234	48 out of 350
Percentage (%)	16.7%	12.98%	12.8%	13.7%
P value		0.0002	0.0006	0.0010

patients (67%) who developed autoantibodies. ABO and Rh phenotype frequencies among the patients in this study are presented in Table 3. The most common blood group was O (177 (49%)) followed by B (111 (30.8%)), A1 (65 (15.4%)), A2 (9 (3%)), and AB (9 (3%)). Prevalence of RhD+ was 88.1% while RhD- was 12.8%.

In the 34 β-thalassemia patients with alloimmunization, 57 alloantibodies were identified and are included in Table 4. Among these, anti-K alloantibody had the highest incidence being detected in 19/57 (33%) patients, followed by anti-E alloantibody (16/57 (28%) patients), anti-C antibody (8/57 (14%) patients), and anti-D and anti-C^w alloantibodies (both being detected in 4/57 (7%) patients). The least prevalent alloantibodies were anti-Jk^a (2/57 (3.5%) patients) and anti-c, and anti-S and anti-Fy^a alloantibodies (in 1/57 (1.8%) patients). Similarly, the prevalence of alloantibodies among β-thalassemia patients revealed that anti-K and anti-E alloantibodies had the highest incidence being detected in 6/13 (46%) and 5/13 (39%) patients, respectively (Table 4).

Table 3: Blood groups of β-thalassemia and sickle cell disease patients in Al-Ahsa Region, Saudi Arabia.

Blood group	Number	%
A	65	15.4
A2	9	3
B	111	30.8
O	177	49
AB	9	3
RhD pos	327	88.1
RhD neg	47	12.8

4. Discussion

RBC alloimmunization and autoimmunization are possible transfusion-related complications. While not all transfusion recipients develop alloantibodies or autoantibodies, RBC alloimmunization and autoimmunization can cause serious morbidity through delayed hemolytic transfusion reactions. In this study, RBC alloimmunization and autoimmunization frequencies were investigated in SCD and β-thalassemia patients in Al-Ahsa Region, Saudi Arabia.

Previous studies have reported varying rates of alloimmunization in Middle Eastern populations ranging from 12.98% to 39.42% in SCD patients and from 13.21% to 35.57% in β-thalassemia patients [16, 17, 21–23]. In the present study, alloimmunization rates were explored in SCD and β-thalassemia patients in Al-Ahsa Region, Saudi Arabia. The alloimmunization rate in chronically transfused β-thalassemia patients was 11.97%, similar to other Saudi studies [17]. However, Hindawi et al. revealed a higher frequency of alloantibodies (39.42%) in a similar study conducted in Jeddah City, Saudi Arabia. In the present study, the alloimmunization rate in SCD patients was 16.7% (Table 2), significantly lower than the rate reported by Hindawi et al. for SCD patients (35.75%).

The low rate of alloimmunization observed in SCD and β-thalassemia patients in the present study could be due to homogeneity of RBC antigens between blood donors and recipients [24]. In the King Fahad Hospital (KFH) in Al-Ahsa, most transfusion-dependent patients and donors are from Al-Ahsa Region. This homogeneity between local patients and donors may be one of the key factors contributing to the low prevalence of alloantibodies. Another possible explanation for the low alloimmunization rates in SCD and β-thalassemia patients is that antigen avoidance via phenotyping is employed at KFH for at-risk patients,

Table 4: Alloantibodies present in β-thalassemia and sickle cell disease patients with alloimmunization in Al-Ahsa Region, Saudi Arabia.

		β-thalassemia		Sickle cell disease		Total	
System	Alloantibody	Number	%	Number	%	Number	%
RH	Anti-D	4	7	N/A	N/A	4	5.7
	Anti-C	8	14	1	7.7	9	12.9
	Anti-c	1	1.8	N/A	N/A	1	1.4
	Anti-E	16	28.1	5	38.5	21	30
	Anti-e	N/A	N/A	1	7.7	1	1.4
	C^w	4	7	N/A	N/A	4	5.7
MNS	Anti-S	1	1.8	N/A	N/A	1	1.4
Lutheran	Anti-Lu^a	1	1.8	N/A	N/A	1	1.4
Kell	Anti-K	19	33.3	6	46.2	25	35.7
Duffy	Anti-Fy^a	1	1.8	N/A	N/A	1	1.4
Kidd	Anti-JK^a	2	3.5	N/A	N/A	2	2.9

including SCD and β-thalassemia patients, prior to RBC transfusions [25].

The present study was also designed to determine the most frequent alloantibodies among chronically transfused patients. In the 34 β-thalassemia patients with alloimmunization, 57 alloantibodies were found anti-K alloantibody (33%), anti-E antibody (28%), anti-C antibody (14%), and anti-D and anti-C^w antibodies (7%). The least prevalent alloantibodies were anti-Jk^a (3.5%), while anti-c, anti-S, and anti-Fy^a (1.8%) were the least detected antibodies. Similar to the prevalence of alloantibodies among β-thalassemia patients, anti-K (46%) and anti-E (39%) had the highest incidence in SCD patients (Table 4). The high frequencies of anti-K alloantibody and anti-E antibody are comparable to previous studies in Saudi Arabia, Egypt, Iran, and Michigan, USA [26].

In this study, the most common blood groups associated with alloimmunization in SCD patients were O RhD positive (41%) and B RhD positive (26%) (Table 4).

Overall, the autoimmunization rate in β-thalassemia patients in this study was 0.7%, significantly lower than rates reported by other studies [14, 15, 17, 21, 23]. The autoimmunization rate in SCD patients (5.3%) was higher than β-thalassemia patients, but significantly lower than rates reported by Halawani et al. (25%). Autoantibodies are frequently encountered during pretransfusion testing and can cause false positive results that may complicate serological compatibility testing to provide safe and compatible blood.

Sickle cell disease and thalassemia are highly prevalent in the Al-Ahsa Region of Saudi Arabia, leading to a large number of patients requiring multiple transfusions [6]. Alloimmunization is a common complication of transfusion therapy in these patients and can result in life-threatening hemolytic reactions. Our study provides important insights into the prevalence of red blood cell alloantibodies in this patient population and highlights the need for improved transfusion protocols to reduce the risk of alloimmunization. We recommend the use of extended phenotyping, including ABO, RH, Kell, Duffy, Kidd, and MNS blood group systems, in transfusion practice for patients with sickle cell disease and thalassemia in the Al-Ahsa Region. In addition, the implementation of a national registry for rare blood donor phenotypes could significantly benefit patients with sickle cell disease and thalassemia by reducing the risk of hemolytic transfusion reactions. Furthermore, the use of molecular genotyping, either alone or in combination with extended phenotyping, may provide a more accurate and comprehensive assessment of a patient's antigen profile, further minimizing the risk of alloimmunization and improving transfusion outcomes. Overall, our study highlights the need for continuous efforts to optimize transfusion protocols for patients with sickle cell disease and thalassemia in the Al-Ahsa Region to reduce the risk of alloimmunization and improve patient outcomes.

5. Conclusion

Blood transfusion-related alloimmunization and autoimmunization compromise the proper management of chronically transfused patients. This study was designed to determine the rates of alloimmunization and autoimmunization in SCD and β-thalassemia patients in Al-Ahsa Region, Saudi Arabia. Alloimmunization and autoimmunization are common among multiple transfused β-thalassemia patients in Saudi Arabia. The most frequent alloantibodies detected in this study were anti-K, anti-E, and anti-C antibodies. Ideally, extended phenotype matching should be implemented to prevent alloimmunization and reduce the risk of developing blood transfusion-related alloantibodies.

Data Availability

The data that support the findings of this study are available from King Fahad Hospital-Al-Hofuf, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of King Fahad Hospital-Al-Hofuf.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

A Case-Control Study of the Factors Associated with Anemia in Chinese Children Aged 3–7 years Old

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Background. Anemia in children is still an important public problem in China and can have a profound impact on the physical and mental health of children. The purpose of this study was to explore the risk factors for anemia among Chinese children aged 3–7 years old and to provide some basis for the prevention and control of anemia. *Methods*. A matched case-control study was conducted and 1104 children (552 cases and 552 controls) were recruited in this study. Cases were children who were diagnosed with anemia by the doctor of physical examination and checked by one deputy chief physician of pediatrics, and controls were healthy children without anemia. Data were collected using a self-designed structured questionnaire. Univariable and multivariable analyses were used to identify independent determinants of anemia. *P* values less than 0.05 were used to declare statistical significance. *Results*. In the multivariable analyses, maternal anemia before or during pregnancy and lactation (OR = 2.14, 95% CI: 1.10~4.15; OR = 2.86, 95% CI: 1.66~4.94; OR = 2.51, 95% CI: 1.13~5.60), gestational weeks (OR = 0.72, 95% CI: 0.53~0.96), having G6PD deficiency or thalassemia (OR = 8.12, 95% CI: 2.00~33.04; OR = 36.25, 95% CI: 10.40~126.43), having cold and cough in previous two weeks (OR = 1.56, 95% CI: 1.04~2.34), family income (OR = 0.80, 95% CI: 0.65~0.97), and being a picky eater (OR = 1.80, 95% CI: 1.20~2.71) were determinants of anemia in children aged 3–7 years old. *Conclusions*. Some of the identified factors are modifiable and could be targeted to reduce childhood anemia. More emphasis should be given by the concerned bodies to intervene in the anemia problem by improving the maternal health education, screening for disease-related anemia, requesting medical services in a timely manner, improving the economic status of households, promoting dietary habits, and improving sanitation and hygiene practices.

1. Introduction

Anemia is regarded as a decrease in the number of red blood cells or their oxygen-carrying capacity. It is also defined as a hemoglobin level below 11 mg/dl for children 6 to 59 months of age [1]. Childhood anemia is a major public health problem worldwide affecting both developing and developed countries [2]. It is associated with adverse effects including impaired immunity and, cognitive development and reduce capacity for work [3–5].

Anemia is a global health problem. In 2008, the World Health Organization (WHO) reported the global anemia prevalence was 47.4% (95% confidence interval [CI] 45.7–49.1) in preschool-age children and 25.4% (95% CI 19.9–30.9) in school-age children. In 2011, one paper reported that 293 million (47%) children younger than 5 years were affected by anemia [6]. In China, the researchers have reported the prevalence of anemia among children between 6% and 27% from 2009 to 2019 [7–10].

The causes of anemia are multifactorial, including shortage of hematopoietic materials [11]. Some reviews have reported the factors related to anemia, such as poor dietary diversity, food insecurity, deworming, maternal anemia, gastrointestinal disease, and educational status [12, 13].

Children are deemed to be at greater risk than other populations [14]. Over the recent years, more attention has been on children. However, many studies related to anemia in children have been cross-sectional, and few analytical studies have been reported. Pingshan is one district of Shenzhen municipality located in the northeast. The economic level is relatively lower, and the migrant population is relatively large. Implementing concrete strategies to reduce is a major task. Therefore, it is important to identify the associated factors to address the problem. To explore factors related to anemia in children, a case-control study was conducted, which could provide support for future anemia prevention and control measures.

2. Methods

2.1. Study Design and Participants. A case-control study was conducted from 2018 to 2020 among children aged 3–7 years old in all kindergartens of Pingshan District, Shenzhen. Every child received physical examination and blood tests at least once a year. All children identified as having anemia by physical examination and HemoCue were included in the case-control study as cases. Then healthy children without anemia were selected as controls from the same class. A case/control rate of 1 : 1 was applied. The matching conditions were the same sex and an age difference of less than 3 months. The sample size was determined by the software of PASS. Assuming a proportion of exposure in cases was 12.0%, a power of 80% and 5% of significance, and odds ratio being assumed to be 1.7, we required 528 cases and 528 controls (1 control per 1 case). In our study, we finally included 552 cases and 552 controls.

2.2. Measurements. Hemoglobin concentration of children was measured using the HemoCue. The operational instructions were strictly obeyed and the outcomes were identified by multiple researchers. Anemia was defined as hemoglobin <110 g/L for children under 59 months or <115 g/L for children over 5 years. Weight and height were measured for all children. The height and weight of children were measured by intelligent physical examination instrument for children (Kangwa Intelligent physical examination instrument). The scales were calibrated each morning and checked at regular intervals throughout the day. All measurements were made by a highly trained research anthropometrist. In addition, a repeated measurement for 10% of the children randomly selected each day was conducted. If the two measurements differed by more than 0.5 cm, a third measurement was taken. When the two measurements were similar, their mean was calculated. Weight-for-age (WAZ), height-for-age (HAZ), and BMI-for-age (BMIZ) z-scores were calculated using the World Health Organization Child Growth Standards Macro for SPSS. Underweight, stunting, and wasting were defined as WAZ < −2.0, HAZ < −2.0, and BMIZ < −2.0 standard deviations (SD), respectively.

2.3. Questionnaire. Self-designed structured questionnaires were administered to children's caregivers to obtain information. The questionnaire's contents mainly included age, sex, ethnicity, birth status, maternal anemia condition, G6PD deficiency, thalassemia, family status, and dietary habits. Trained interviewers conducted face-to-face interviews with the main caregivers. All caregivers participated on a voluntary basis and were not remunerated for their contribution.

2.4. Data Analysis. The information was recorded in a database using Excel. The data was cleaned and analyzed using Stata 16.0. Simple frequencies and percentages were used for categorical variables. Univariable conditional logistic regression was used to determine the association of independent variables with the dependent variable. Using a manual stepwise forward selection of variables, significant variables were put in the multivariable conditional logistic models, one at a time, to check for significant association until a final model of significant variables was achieved. A P value equal to or less than 0.05 was considered statistically significant.

3. Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board (IRB) of Shenzhen Pingshan Maternal and Child Health Hospital and complied with the national legislation and the Declaration of Helsinki guidelines. Informed written consent was obtained from the caregivers who agreed to participate in this study, and their participation was voluntary.

4. Results

4.1. Characteristics. A total of 552 children and 552 controls were enrolled in the study. There were 55.62% (307/552) males and 44.38% (245/552) females in both the case group and the control group. The mean ages for the cases and controls were 5.19 ± 0.80 years and 5.21 ± 0.79 years, respectively, and their age ranged between 3 and 7 years. There was no difference in the two matched variables including sex and age between the two groups. Greater than 90% of children, mothers, and fathers were of Han nationality in the two groups. The mean ages of the mothers were 32.77 ± 4.26 years and 32.42 ± 4.73 years for the case and control groups. The mean ages of the fathers were 34.86 ± 5.20 years and 32.99 ± 4.83 years for the case and control groups. More than 50% of children's parents had an educational level of senior high school or above in cases and controls (Table 1).

4.2. Univariable Analysis of Determinants of Anemia in Children Aged 3–7 years Old. Table 2 shows the results of univariable analysis conducted between anemia and each of the independent variables. Children in the East were likely to develop anemia than children in the West (OR = 1.86, 95% CI: 1.22~2.86). Ethnic minority students and parents were prone to anemia compared with Han nationality (children: OR = 1.73, 95% CI: 1.02~2.92; mother: OR = 1.76, 95% CI: 1.08~2.88; father: OR = 1.92, 95% CI: 1.17~3.14). Parents with higher education could decrease the risk of anemia in children (mother: OR = 0.84, 95% CI: 0.73~0.97; father: 0.79,

Table 1: Baseline characteristics of children.

	Cases (n, %)	Control (n, %)	Total (n, %)
Sex			
Male	307 (55.62)	307 (55.62)	614 (55.62)
Female	245 (44.38)	245 (44.38)	490 (44.38)
Age of children (years)	5.19 ± 0.80	5.21 ± 0.79	5.20 ± 0.80
Ethnicity of children			
Han	513 (92.93)	529 (95.83)	1042 (94.38)
Minorities	39 (7.07)	23 (4.17)	62 (5.62)
Ethnicity of mothers			
Han	508 (92.03)	527 (95.47)	1035 (93.75)
Minorities	44 (7.97)	25 (4.53)	69 (6.25)
Age of mothers (years)	32.77 ± 4.26	32.42 ± 4.73	32.60 ± 4.50
Mothers' education			
Junior high school and below	196 (35.61)	164 (29.71)	360 (32.61)
High school and secondary specialized school	157 (28.44)	175 (31.70)	332 (30.07)
Junior college	136 (24.64)	126 (22.83)	262 (23.73)
Bachelor degree and above	63 (11.41)	87 (15.76)	150 (13.59)
Age of fathers (years)	34.86 ± 5.20	34.86 ± 5.20	34.92 ± 5.02
Ethnicity of fathers			
Han	505 (91.49)	527 (95.47)	1032 (93.48)
Minorities	47 (8.51)	25 (4.53)	72 (6.52)
Fathers' education			
Junior high school and below	168 (30.43)	128 (23.19)	296 (26.81)
High school and secondary specialized school	168 (30.43)	180 (32.61)	348 (31.52)
Junior college	117 (21.20)	110 (19.93)	227 (20.56)
Bachelor degree and above	99 (17.93)	134 (24.82)	233 (21.11)

95 CI: 0.69~0.91). Maternal anemia before pregnancy or during pregnancy or nursing period could increase the risk of anemia in children (before pregnancy: OR = 8.57, 95% CI: 5.56~13.19; pregnancy: OR = 6.04, 95% CI: 4.32~8.45; nursing period: OR = 6.39, 95% CI: 4.54~9.00). Mothers' active or passive exposure to smoke during pregnancy would increase the risk of anemia in children (OR = 2.64, 95% CI: 1.32~5.28). Higher birth weight and height would reduce the risk of anemia in children (birth weight: OR = 0.53, 95% CI: 0.31~0.92; birth height: OR = 0.92, 95% CI: 0.86~0.98). Greater gestational age could reduce the risk of anemia in children (OR = 0.75, 95% CI: 0.63~0.90). Mothers with spontaneous abortion could increase the risk of anemia in children (OR = 1.96, 95% CI: 1.28~3.03). Children with G6PD deficiency or thalassemia could increase the risk of anemia in children (G6PD deficiency: OR = 6.00, 95% CI: 2.53~14.24; thalassemia: OR = 48.00, 95% CI: 15.30~151.58). Children having cold and cough in recent two previous weeks would increase the risk of anemia (OR = 1.42, 95% CI: 1.10~1.83). Higher family income likely decreased the risk of anemia in children (OR = 0.80, 95% CI: 0.70~0.91). Children eating for more than 30 min were prone to anemia (OR = 1.63, 95% CI: 1.28~2.09). Children being picky eaters were likely to be anemic (OR = 2.2, 95% CI: 1.69~2.87). Children who like eating snacks were more likely to become anemic (OR = 1.37, 95% CI: 1.03~1.80). Similarly, children eating with no attention were likely to develop anemia (OR = 1.74, 95% CI: 1.33~2.26).

Mothers' age, times of pregnancies, times of birth, mothers' consumption of tea during pregnancy, mode of delivery, diarrhea in recent weeks, trauma in the previous two weeks, permanent household population, consumption of dietary supplements containing iron, giving tea or milk to the children, cooking alone for the children, receiving childcare guidance, stunting, underweight, and wasting were not associated with anemia ($p > 0.05$).

4.3. Multivariable Analysis of Determinants of Anemia in Children Aged 3–7 years Old. The multivariable analysis (Table 3) identified an association between maternal anemia before or during pregnancy and lactation and more children having anemia (before pregnancy: OR = 2.14, 95% CI: 1.10 ~ 4.15; during pregnancy: OR = 2.86, 95% CI: 1.66 ~ 4.94; lactation: OR = 2.51, 95% CI: 1.13~5.60). Mothers with greater gestational age could reduce the risk of anemia (OR = 0.72, 95% CI: 0.53~0.96). G6PD deficiency or thalassemia in children was strongly associated with anemia in children (G6PD deficiency: OR = 8.12, 95% CI: 2.00~33.44; thalassemia: OR = 36.25, 95% CI: 10.40~126.43). Cold and cough in children in previous two weeks was significantly associated with an increased risk of anemia in children (OR = 1.56, 95% CI: 1.04~2.34). Children with a higher income were less likely to have anemia (OR = 0.80, 95% CI: 0.65~0.97). Children who were picky about food were prone to anemia (OR = 1.80, 95% CI: 1.20~2.71).

5. Discussion

In China, the program for the development of children was implemented by the government and, has been working to solve the problem of anemia in children. Under this background, identifying the risk factors related to anemia is a very important task for eliminating anemia. Analytic

Table 2: Univariable analysis of determinants of anemia in children.

	Cases (n, %)	Control (n, %)	*P*	OR (95% CI)
Children's region				
Western region	46 (8.33)	63 (11.41)		1
Central region	134 (24.28)	195 (35.33)	0.982	1.00 (0.65~1.55)
Eastern region	372 (67.39)	294 (53.26)	0.004	1.86 (1.22~2.86)
Ethnicity of children				
Han	513 (92.93)	529 (95.83)		1
Minorities	39 (7.07)	23 (4.17)	0.041	1.73 (1.02~2.92)
Ethnicity of mothers				
Han	508 (92.03)	527 (95.47)		1
Minorities	44 (7.97)	25 (4.53)	0.024	1.76 (1.08~2.88)
Age of mothers (years)	32.77 ± 4.26	32.42 ± 4.73	0.192	0.98 (0.96~1.01)
Mothers' education			0.015	0.84 (0.73~0.97)
Junior high school and below	196 (35.61)	164 (29.71)		
High school and secondary specialized school	157 (28.44)	175 (31.70)		
Junior college	136 (24.64)	126 (22.83)		
Bachelor degree and above	63 (11.41)	87 (15.76)		
Ethnicity of fathers				
Han	505 (91.49)	527 (95.47)		1
Minorities	47 (8.51)	25 (4.53)	0.010	1.92 (1.17~3.14)
Fathers' education			0.001	0.79 (0.69~0.91)
Junior high school and below	168 (30.43)	128 (23.19)		
High school and secondary specialized school	168 (30.43)	180 (32.61)		
Junior college	117 (21.20)	110 (19.93)		
Bachelor degree and above	99 (17.93)	134 (24.82)		
Times of pregnancy				
<3	401 (72.64)	426 (77.17)		1
≥3	151 (27.36)	126 (22.83)	0.076	1.30 (0.97~1.71)
Times of birth				
1	183 (33.15)	200 (36.23)		1
2	310 (56.16)	301 (54.53)	0.322	1.14 (0.88~1.48)
≥3	59 (10.69)	51 (9.24)	0.245	1.30 (0.83~2.03)
Maternal anemia before pregnancy				
Yes	221 (40.04)	47 (8.51)	<0.001	8.57 (5.56~13.19)
No	331 (59.96)	505 (91.49)		1
Maternal anemia during pregnancy				
Yes	290 (52.06)	87 (15.62)	<0.001	6.04 (4.32~8.45)
No	267 (47.94)	470 (84.38)		1
Maternal anemia during nursing period				
Yes	290 (52.54)	85 (15.40)	<0.001	6.39 (4.54~9.00)
No	262 (47.46)	467 (84.60)		1
Mothers smoked actively or passively during pregnancy				
Yes	32 (5.80)	14 (2.54)	0.006	2.64 (1.32~5.28)
No	520 (94.20)	538 (97.46)		
Mothers drank tea during pregnancy				
Yes	44 (7.97)	32 (5.80)	0.154	1.41 (0.88~2.27)
No	508 (92.03)	520 (94.20)		
Birth weight (g)			0.023	0.53 (0.31~0.92)
<2500	14 (2.54)	11 (1.99)		
2500~4000	528 (95.65)	516 (93.48)		
>4000	10 (1.81)	25 (4.53)		
Birth height (cm)	50.07 ± 2.02	50.32 ± 1.84	0.017	0.92 (0.86~0.98)
Gestational weeks			0.002	0.75 (0.63~0.90)
<37	31 (5.62)	21 (3.80)		
37~38	149 (26.99)	117 (21.20)		
39~40	320 (57.97)	342 (61.96)		
>40	52 (9.42)	72 (13.04)		
History of spontaneous abortion of mother				
Yes	69 (12.50)	39 (7.07)	0.002	1.96 (1.28~3.03)

Table 2: Continued.

	Cases (n, %)	Control (n, %)	*P*	OR (95% CI)
No	483 (87.50)	513 (92.93)		
Mode of delivery				
Spontaneous labor	379 (68.66)	355 (64.31)		1
Cesarean section	173 (31.34)	197 (35.69)	0.116	0.81 (0.63~1.05)
G6PD deficiency of children				
Yes	38 (6.88)	8 (1.45)	<0.001	6.00 (2.53~14.24)
No	514 (93.12)	544 (98.55)		1
Thalassemia of children				
Yes	146 (26.45)	5 (0.91)	<0.001	48.00 (15.30~151.58)
No	406 (73.55)	547 (99.09)		1
Diarrhea in recent weeks				
Yes	6 (1.09)	4 (0.72)	0.530	1.50 (0.42~5.32)
No	546 (98.91)	548 (99.28)		1
Cold and cough in previous two weeks				
Yes	244 (44.20)	201 (36.41)	0.006	1.42 (1.10~1.83)
No	308 (55.80)	351 (63.59)		1
Trauma in previous two weeks				
Yes	4 (0.72)	1 (0.18)	0.215	4.00 (0.45~35.79)
No	548 (99.28)	551 (99.82)		1
Permanent household population				
≤4	264 (47.83)	243 (44.02)		
>4	288 (52.17)	309 (55.98)	0.209	0.86 (0.68~1.09)
Family income (RMB/moth)			0.001	0.80 (0.70~0.91)
<3000	50 (9.06)	32 (5.80)		
3000~5999	220 (39.86)	191 (34.60)		
6000~8999	105 (19.02)	115 (20.83)		
≥9000	177 (32.07)	214 (38.77)		
Consumption of iron supplements				
Yes	272 (49.28)	288 (52.17)		1
No	280 (50.72)	264 (47.83)	0.316	1.13 (0.89~1.45)
Giving tea to the children				
Yes	41 (7.43)	37 (6.70)	0.642	1.11 (0.71~1.76)
No	511 (92.57)	515 (93.30)		1
Giving milk to the children				
Yes	499 (90.40)	506 (91.67)	0.448	0.85 (0.55~1.30)
No	53 (9.60)	46 (8.33)		1
Cooking alone for the children				
Yes	386 (69.93)	395 (71.56)		1
No	166 (30.07)	157 (28.44)	0.539	1.09 (0.83~1.42)
Children eating for more than 30 min				
Yes	325 (58.88)	259 (46.92)	<0.001	1.63 (1.28~2.09)
No	227 (41.12)	293 (53.08)		1
Picky eater				
Yes	385 (69.75)	289 (52.63)	<0.001	2.2 (1.69~2.87)
No	167 (30.25)	263 (47.64)		1
Like eating snacks				
Yes	418 (75.72)	386 (69.93)	0.026	1.37 (1.03~1.80)
No	134 (24.28)	166 (30.07)		
Eating with no attention				
Yes	408 (73.91)	344 (62.32)	<0.001	1.74 (1.33~2.26)
No	144 (26.09)	208 (37.68)		
Receiving childcare guidance				
Yes	223 (40.40)	249 (45.11)		1
No	329 (59.60)	303 (54.89)	0.105	1.23 (0.96~1.57)
Stunting			0.060	1.7 (0.98~2.95)
Yes	39 (7.07)	25 (4.53)		
No	513 (92.93)	527 (95.47)		

Table 2: Continued.

	Cases (n, %)	Control (n, %)	*P*	OR (95% CI)
Underweight			0.213	0.63 (0.31~1.30)
Yes	12 (2.17)	19 (3.44)		
No	540 (97.83)	533 (96.56)		
Wasting			0.198	1.64 (0.77~3.46)
Yes	19 (3.44)	12 (2.17)		
No	533 (96.56)	540 (97.83)		

Table 3: Multivariable analysis of determinants of anemia in children.

Variables	b	SE	*P*	OR (95% CI)
Maternal anemia before pregnancy	0.76	0.34	0.025	2.14 (1.10~4.15)
Maternal anemia during pregnancy	1.05	0.28	<0.001	2.86 (1.66~4.94)
Maternal anemia during nursing period	0.92	0.41	0.024	2.51 (1.13~5.60)
Gestational weeks	-0.34	0.15	0.024	0.72 (0.53~0.96)
G6PD deficiency	2.10	0.72	0.003	8.12 (2.00~33.04)
Having thalassemia	3.59	0.64	<0.001	36.25 (10.40~126.43)
Cold and cough in previous two weeks	0.45	0.21	0.031	1.56 (1.04~2.34)
Family income (RMB/month)	-0.22	0.10	0.026	0.80 (0.65~0.97)
Picky eater	0.59	0.21	0.005	1.80 (1.20~2.71)

research, such as case-control studies, could provide more reliable predictors to guide the prevention and control of anemia in children.

Maternal anemia was consistently related to the occurrence of childhood anemia. The study showed that children whose mothers had anemia before or during pregnancy and nursing period were more likely to develop anemia than those whose mothers did not have anemia during that time. This finding was consistent with the results from Leite MS [15], as mothers and children were most often mutually exposed to a common set of physical, socioeconomic, and dietary conditions. Besides, Catherine Smith [16] suggested that maternal anemia would increase the risk of preterm birth. Children born prematurely have a higher risk of anemia in childhood. Similarly, we discovered that mothers with greater gestational weeks could decrease the risk of anemia in children.

We also found that genetic diseases, such as thalassemia and G6PD deficiency, might increase the risk of anemia in children. In our study, children with thalassemia had the highest risk of developing anemia, with odds ratio of 34.26. Children with G6PD deficiency also had an increased risk of anemia, with an odds ratio of 8.78. Similarly, a study from Philippe Joly [17] reported that these two kinds of genetic diseases were associated with children developing anemia. Because of enzyme genetic deficiency or gene mutation, these two genetic diseases may lead to varying degrees of hemolysis in children, resulting in anemia.

In addition, we found that children with cold and cough in the previous two weeks were prone to anemia. Children with recurrent respiratory infections are more susceptible to anemia [18]. Therefore, when children develop respiratory symptoms such as colds and coughs, parents should seek medical services in a timely manner and take effective intervention measures to reduce the occurrence of adverse effects.

We also discovered that children's family economic level and living habits were important factors of influencing anemia in children. In this study, the higher the family income was, the less likely children were to develop anemia. A similar study reported that the odds of children with a lower family income having iron deficiency anemia were 3 times higher than those of children in the highest family income group [19]. Moreover, children who were picky eaters were prone to anemia. A meta-analysis also reported that poor food diversity was an important predictor of anemia in children under 5 [12]. Therefore, children with higher economic families might be more easily to acquire diversified food, good health education, and develop good living habits that protect them from anemia.

There were some limitations to this study. First, we could not determine the prevalence of anemia, so we could not compare the status of subgroups. Second, some information bias may have occurred in this study because some data were obtained from past information. Third, the factors associated with different types of anemia were not identified in this study. Four, some variables (e.g., dietary intake) were not included because of the limited resources.

6. Conclusions

In this study, anemia was significantly associated with maternal anemia, gestational weeks, G6PD deficiency, thalassemia, cold and cough in the previous two weeks, family income, and being a picky eater. Deeper knowledge about the etiology of anemia in this region is essential to its proper treatment and prevention.

Abbreviations

OR: Odds ratio
CI: Confidence interval
G6PD: Glucose-6-phosphate dehydrogenase.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interests.

Authors' Contributions

JM and HZ made substantial contributions to the conception and design of the study and were involved in writing and drafting the manuscript. ZF coordinated data collection and personnel training. SH, ZW, and CZ were responsible for performing the research and data collection, analysis, and interpretation. YW participated in the revision of the manuscript. All authors read and approved the final manuscript.

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Review Article

A Review of the Risk Factors for Iron Deficiency Anaemia among Adolescents in Developing Countries

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Introduction. Identifying the root causes of iron deficiency anaemia is a prerequisite for effective management and prevention in adolescents. This systematic review assessed risk factors of iron deficiency anaemia among adolescents living in developing countries. *Method*. Electronic databases such as PubMed, Cochrane Library, Science Direct, Google Scholar, and SCOPUS were comprehensively searched for studies published between 1990 and 2020 that involved risk factors of iron deficiency anaemia among adolescents living in developing countries. The quality of the included studies was assessed using the American Dietetic Association Quality Criteria Checklist. *Results*. A total of 2,252 publications were reviewed, and only fifteen cross-sectional studies were eligible for inclusion, eight of which focused on female adolescents and seven on both genders. Direct risk factors contributing to anaemia among adolescents included food intake practices ($n = 10$ studies), female adolescents ($n = 8$ studies), menstruation ($n = 5$ studies), and parasitic infection ($n = 6$ studies). Indirect risk factors found to be associated with anaemia among adolescents included low educational status ($n = 4$ studies) and low socioeconomic status ($n = 3$ studies). All fifteen studies were of good quality. *Conclusion*. Food intake practices, female adolescents, menstruation, parasitic infection, and low educational status were the leading risk factors of iron deficiency anaemia among adolescents. Further research should concentrate on assessing the effectiveness and efficacy of existing interventions aimed at preventing iron deficiency among vulnerable groups in developing countries.

1. Introduction

Adolescents undergo physiological and psychological growth to set the foundation of adulthood. The biological well-being of adolescents requires improved nourishment. It has been revealed that prolonged insufficient intake of foods rich in micronutrients such as iron, zinc, and vitamin A relevant to support the biological metamorphosis in adolescents can adversely affect their growth and well-being [1]. The majority of adolescents habitually skip breakfast, fruits, vegetables, and milk daily, reducing their dietary intake [2, 3]. Adolescents with such dietary practices manifest micronutrient inadequacies such as iron, calcium, zinc, folic acid, and vitamins A, D, and C [4, 5]. These deficiencies expose adolescents to perpetual nutritional and health vulnerabilities.

Deficiencies of iron, folate, and vitamin B_{12} contribute to nutritional anaemia in adolescents [6, 7]. Among the different types of nutritional anaemias, iron deficiency anaemia is the most prevalent [8–10]. Iron deficiency anaemia (IDA) is measured with indicators such as haemoglobin, serum ferritin, transferrin receptors, transferrin saturation/total iron binding capacity, and zinc protoporphyrin [11, 12]. Anaemia is mostly defined as low haemoglobin levels in the blood or haemoglobin levels less than 120 g/l in adolescents [13].

Statistics show that about 30–35% of the world's population suffers from iron deficiency anaemia, which affects

about 47.5% of people living in Africa [7, 14]. Populations most at risk of iron deficiency anaemia are children aged less than five years, adolescents, women of reproductive age, pregnant women, and lactating mothers [14].

To ameliorate the prevalence and consequences of iron deficiency anaemia in adolescents, a review study recommended the identification of localized risk factors of iron deficiency anaemia to aid in effective management and prevention [15]. Predictors of iron deficiency anaemia among adolescents have been reported by different studies in several countries [16–18]. In developing countries, risk factors of IDA include but are not limited to malaria, worm infestation, low dietary iron intake, micronutrient deficiencies, the human immunodeficiency virus, and inherited disorders [19]. The wide variety of contributory factors of IDA reported by many studies negatively impacts adolescent's health. Due to this, several interventions have failed to reduce the high prevalence of IDA among adolescents in the long term.

Iron deficiency anaemia negatively impacts the educational and economic well-being of adolescents. It has been associated with stunting, wasting, being underweight, poor cognitive function, low physical activity, and attention deficit hyperactive disorders in adolescents [20–26]. Iron deficiency anaemia is now known to be the leading cause of disability adjusted live years in adolescents [27].

To successfully address iron deficiency anaemia, it is critical to holistically identify the key risk factors affecting adolescents that contribute to this deficiency. The systematic review assessed the risk factors of iron deficiency anaemia among adolescents living in developing countries.

2. Method

2.1. Study Design and Search Strategy. This systematic review was conducted following the guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [28]. The current review defined an adolescent as an individual with an age ranging from 10 to 19 years [29]. The list of developing countries considered was based on country classifications by the United Nations Children's Fund [30]. A comprehensive search of articles published from January 1990 to December 2020 was sourced from Google Scholar, PubMed, Scopus, Science direct, and Cochrane Library. The search terms used either singly or in combination included risk factors of anaemia, iron deficiency anaemia, determinants of anaemia, predictors of anaemia, anaemia in adolescents, low haemoglobin, anaemia, and adolescents.

2.2. Study Selection and Eligibility Criteria. The review focused on studies with the primary objective of identifying risk factors of iron deficiency anaemia (IDA) among adolescents living in developing countries. Studies conducted among adolescents without any underlying health conditions were included. Research conducted among adolescents with pregnancy, lactating, sickle cell, or genetic haemoglobin or with any underlying condition, age group mixed, and other forms of anaemia were excluded. Studies with inaccessible full articles, non-English written articles, and articles published before 1990 were also excluded.

2.3. Outcomes Assessed. The outcomes assessed in this review were risk factors of iron deficiency anaemia among adolescents. The primary outcomes were the risk factors directly associated with adolescents contributing to iron deficiency anaemia. The secondary outcomes were risk factors indirectly associated with adolescents, leading to iron deficiency anaemia.

2.4. Data Extraction and Synthesis. The primary information from each study was extracted by one researcher. The primary information for the review included the following: author (s), country, year, gender, age, sample size, and risk factors of iron deficiency anaemia. The data are summarized in Table 1.

2.5. Quality Assessment. The methodological quality assessment of each study was checked using the American Dietetic Association Quality Criteria Checklist [46]. The overall quality of each study was rated positive, negative, or neutral. The findings of the quality assessments are shown in Table 2.

3. Result

3.1. Study Selection. A total of 2,252 articles were retrieved from the five databases. Six hundred and eighteen (618) duplicates were removed and one thousand, four hundred and ninety-two (1,492) records were excluded after screening by title and abstract. One hundred and forty-two (142) articles were fully assessed for eligibility, and one hundred and twenty-seven (127) articles were also excluded based on the inclusion and exclusion criteria. Finally, fifteen (15) studies were included in the review (Figure 1).

3.2. Study Characteristics. All studies included in this review were cross-sectional and published between the years 1990 and 2020. Five studies were conducted in Ethiopia [31, 32, 34, 36, 38]; four studies were also conducted in India [37, 39, 40, 43]; two studies were conducted in Kenya [41, 44]; and one study was conducted in Ghana [33], Egypt [45], Nepal [35], and Iran [42]. Only two of the studies had nationwide representation [35, 45]. Eight of the studies recruited exclusively female adolescents and seven of the studies recruited adolescents of mixed gender. The studies had sample sizes ranging from 137 to 2,032. Participants were aged 10–19 years (Table 1).

3.3. Assessment of the Study Quality. Table 2 shows the quality assessment of the studies using the quality control checklist. All studies were cross-sectional, and attributes of the quality criteria checklist were modified for maximum use in assessment. Attributes such as "comparable study groups"

Table 1: Summary of studies included in the systematic review.

Study details	Year	Study design	Gender and age (years)	Sample size	Summary of results
Fentie et al. [31]; Ethiopia	2019	Cross-sectional	Girls; 14–19	528	Adolescent girls living alone (AOR = 4.430, 95% CI = 2.20–8.90)*, low dietary diversity score (AOR = 3.57, 95% CI = 1.88–6.75)*, excessive menstrual bleeding (AOR = 2.25, 95% CI = 1.17–4.33)*, and low economic status (AOR = 2.16, 95% CI = 1.17–4.33)* were positively associated with anaemia
Fage et al. [32]; Ethiopia	2017	Cross-sectional	Both; 10–19	493	Female adolescent (AOR = 2.31, 95% CI = 1.51–3.54)*, low educational status of adolescent (AOR = 1.66, 95% CI = 1.004–2.77)*, illiterate mothers (AOR = 2.23, 95% CI = 1.02–4.89)*, and low dietary diversity score (AOR = 2.33, 95% CI = 1.12–4.86)* increased odds of anaemia
Wiafe et al. [33]; Ghana	2019	Cross-sectional	Both; 10–14	137	Meal skipping (OR = 1.4, 95% CI = 0.7–3.0), snacking (OR = 1.6, 95% CI = 0.7–3.6), and adolescent with JHS education (OR = 1.7, 95% CI = 0.7–4.0) were positively associated with anaemia
Gebreyesus et al. [34]; Ethiopia	2015	Cross-sectional	Girls; 10–19	1323	Early adolescents (AOR = 1.98, 95% CI = 1.03–3.82)* and food insecure household (AOR = 1.48, 95% CI = 1.05–2.049)* increased the risk of anaemia
Chalise et al. [35]; Nepal	2014	Cross-sectional	Both; 10–19	3780	Older adolescents (AOR = 1.75, 95% CI = 1.44–2.13)*, female adolescents (AOR = 2.02, 95% CI = 1.57–2.60)*, and walking barefooted (AOR = 1.78, 95% CI = 1.08–2.94) increased risk of anaemia
Shaka and Wondimagegne [36]; Ethiopia	2016	Cross-sectional	Both; 10–19	443	Early adolescents (AOR = 4.75, 95% CI = 1.69–13.35)*, large family size (AOR = 9.82, 95% CI = 2.42–39.88), adolescents living in rural areas (AOR = 4.37, 95% CI = 1.54–12.46), and lower meal frequency (AOR = 3.25, 95% CI = 1.42–7.45) increased the odds of anaemia
Ahankari et al. [37]; India	2014–2015	Cross-sectional	Girls; 13–17	1,010	Anaemia was associated with older adolescents (AOR = 1.41, 95% CI = 1.17–1.70)*
Regasa and Haidar [38]; Ethiopia	2016	Cross-sectional	Girls; 10–19	448	Late adolescent (AOR = 3.8, 95% CI = 2.3–8.5)*, adolescents living in rural areas (AOR = 3.4 95% CI = 1.9–7.0)*, and menarche (AOR = 2.3 95% CI = 1.34–4.2)* increased odds of anaemia
Agrawal et al. [39]; India	2014–2015	Cross-sectional	Both; 10–19	526	Religion (Muslim) (AOR = 1.4, 95% CI = 0.82–2.43), female gender (AOR = 1.9, 95% CI = 1.3–2.7)*, illiterate mothers (AOR = 1.42, 95% CI = 0.62–3.24), vegetarian diet (AOR = 2.28, 95% CI = 0.83–6.22), and occupation (student) (AOR = 2.86, 95% CI = 1.16–7.04)* increased risk of anaemia
Thomas et al. [40]; India	2011–2013	Cross-sectional	Both; 10–18	200	Female gender (OR = 1.70, 95% CI = 0.84–3.43), vegetarian diet (OR = 4.41, 95% CI = 2.04–9.51)*, and history of worm infestation (OR = 2.08, 95% CI = 0.96–4.50) * contributed to anaemia
Nelima [41], Kenya	2015	Cross-sectional	Girls; 14–18	230	Inadequate iron intake (OR = 10.3, 95% CI = 5.2–20.37)*, late adolescents (OR = 2.69, 95% CI = 1.46–4.96)*, malaria infections (OR = 5.38, 95% CI = 2.84–10.19)*, and parasitic infections (OR = 11.94, 95% CI = 2.71–52.57)* were positively associated with anaemia
Ramzi et al. [42]; Iran	2011	Cross-sectional	Girls; 10–19	363	Parasitic infections (OR = 6.83, 95% CI = 1.66–28.11)*, large family size (OR = 2.25, 95% CI = 0.91–5.52)*, and longer duration of menstruation (OR = 1.78, 95% CI = 0.64–4.93) were associated with anaemia
Kaur et al. [43]; India	2000–2002	Cross-sectional	Girls; 13–19	630	Vegetarian diet (OR = 5.83, 95% CI = 3.73–9.13)*, excessive menstrual bleeding (OR = 5.65, 95% CI = 1.26–25.38)*, low iron intake (OR = 4.16, CI = 2.08–8.31)*, and history of worm infestation (OR = 4.11, CI = 1.70–9.93)* increased odds of anaemia

Table 1: Continued.

Study details	Year	Study design	Gender and age (years)	Sample size	Summary of results
Leenstra et al. [44]; Kenya	1998–1999	Cross-sectional	Girls; 12–18	648	Heavy menstrual bleeding (OR = 4.29, 95% CI = 1.46–12.64)* and parasitic infections (OR = 2.01 95% CI = 1.02–3.98)* were positively associated with anaemia
El Sahn et al. [45]; Egypt	1997	Cross-sectional	Both; 10–19	1,980	Low educational status (OR = 3.46, 95% CI = 1.90–6.32)*, low socioeconomic status (OR = 1.43, 95% CI = 1.13–1.81)*, and increased risk of anaemia

*p value is significant.

Table 2: Quality assessment of the studies using quality control checklist.

Study	Clear research question	Participant selection free from bias	Comparable study groups	Participant withdrawals or response rate described	Use of blinding	Description of intervention protocol and/or data collection procedures	Outcomes clearly defined	Appropriate statistical analysis	Conclusions supported by results	Unlikely funding bias	Overall quality rating
Fentie et al. [31]	+	+	N/A	+	N/A	+	+	+	+	+	+
Fage et al. [32]	+	+	N/A	+	N/A	+	+	+	+	+	+
Wiafe et al. [33]	+	+	N/A	+	N/A	+	+	+	+	+	+
Gebreyesus et al. [34]	+	+	N/A	+	N/A	+	+	+	+	+	+
Chalise et al. [35]	+	+	N/A	−	N/A	+	+	+	+	+	+
Shaka and Wondimagegne [36]	+	+	N/A	+	N/A	+	+	+	+	+	+
Ahankari et al. [37]	+	+	N/A	+	N/A	+	+	+	+	+	+
Regasa and Haidar [38]	+	+	N/A	+	N/A	+	+	+	+	+	+
Agrawal et al. [39]	+	+	N/A	+	N/A	+	+	+	+	+	+
Thomas et al. [40]	+	−	N/A	+	N/A	+	+	+	+	+	+
Nelima [41]	+	+	N/A	−	N/A	+	+	+	+	NR	+
Ramzi et al. [42]	+	+	N/A	−	N/A	+	+	+	+	+	+
Kaur et al. [43]	+	+	N/A	+	N/A	+	+	+	+	NR	+
Leenstra et al. [44]	+	+	N/A	+	N/A	+	+	+	+	+	+
El Sahn et al. [45]	+	+	N/A	+	N/A	+	+	+	+	+	+

N/A, not applicable (due to cross-sectional design of study); NR, not reported. +, positive overall score: this overall score is given if criteria 2, 3, 6, and 7 of the QCC and one additional criterion have received a positive score. Ø, neutral overall score: this score is given if more criteria are met than for a negative overall score, but an overall positive score is not reached. −, negative overall score: this score is given if six or more QCC criteria are not met.

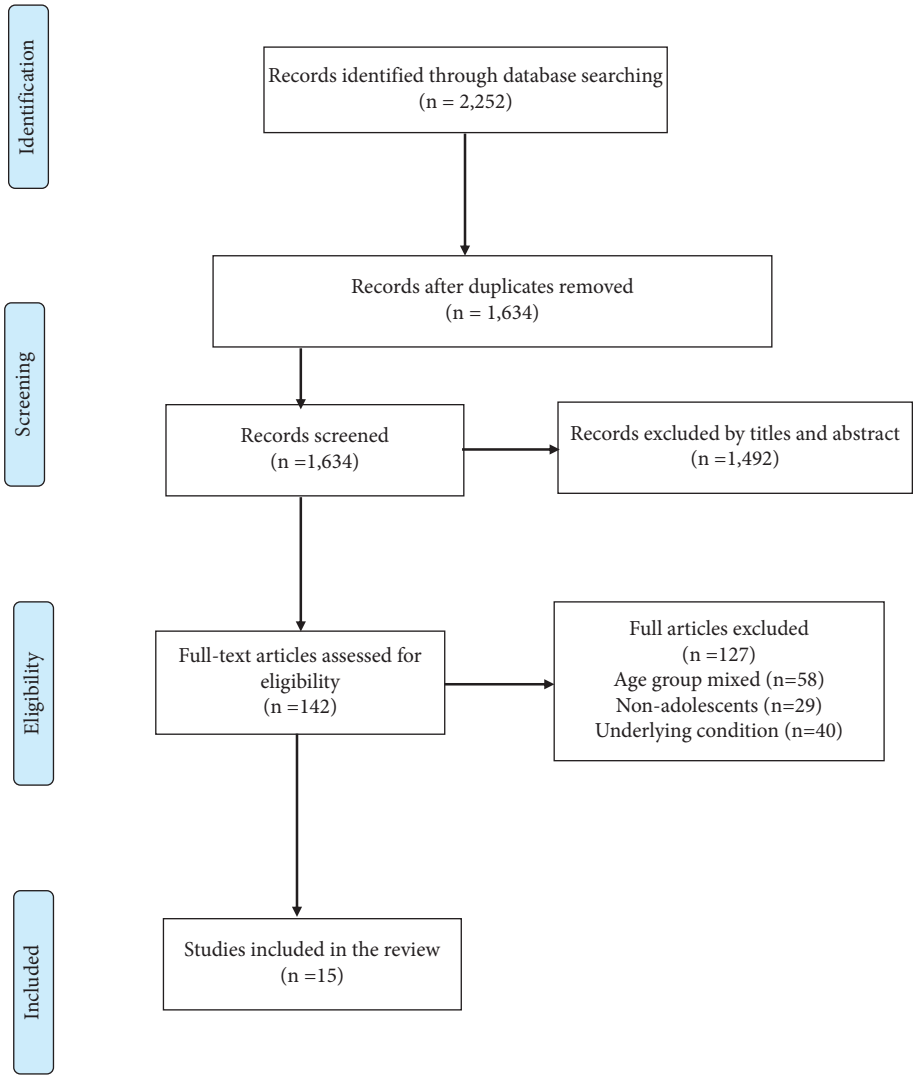

Figure 1: PRISMA diagram of the review.

and "use of blinding" were not applicable for the assessment of the studies. All fifteen studies had a positive quality rating.

3.4. Associated Factors of Adolescent Iron Deficiency Anaemia. The various studies assessed different factors contributing to iron deficiency anaemia among adolescents in developing countries. For this review, the factors have been grouped under direct factors: food intake practices, malaria infection, worm infestation, female adolescents, blood loss, and indirect factors: educational status, socioeconomic status, rural areas, family size, religion, and walking barefoot (Figure 2).

3.5. Food Intake Practices. Ten studies assessed the relationship between iron deficiency anaemia and food intake practices among adolescents. Three of these studies indicated that vegetarian dietary practices increased the odds of anaemia among adolescents [39, 40, 43]. Kuar et al. [42] reported that vegetarian adolescents had higher odds of being anaemic than those who consumed a mixed diet (OR = 8.5, 95% CI = 5.7–12.8). In another cross-sectional study, vegetarian adolescents had a 4.4% greater chance of being anaemic than their counterparts who did not practice vegetarianism [40]. Two studies reported on dietary diversity. The studies documented that low dietary diversity significantly increased adolescents' risk (AOR = 3.57, 95% CI: 1.88–6.75) [31] and (AOR = 2.33, 95% CI: 1.2–4.86) [32] of being anaemic. Furthermore, low dietary iron intake significantly increased anaemia among adolescents [41, 43]. Two studies reported on meal skipping and meal frequency [33, 36]. Adolescents who skipped meals and had a low meal frequency had high chances of being anaemic. One study among adolescents in Ghana showed that snacking was not significantly associated with anaemia ($\beta = 0.484$, $p > 0.05$) [33].

3.6. Parasitic Infections. Six studies reported on parasitic infections. Malaria and worm infestations, particularly schistosomiasis and ova ascaris, were the common parasitic infections found among adolescent girls in the studies

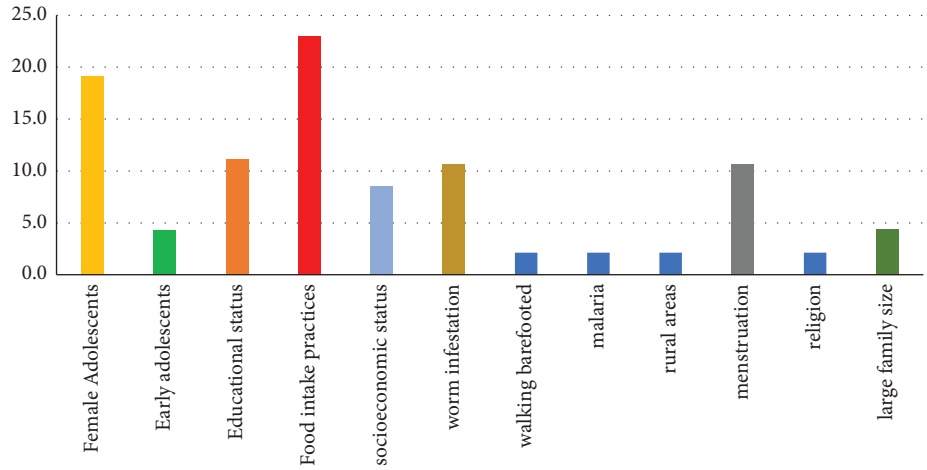

FIGURE 2: Risk factors of anaemia. Education: low maternal education[1] and adolescent; food intake practices: vegetarian diet[1], low dietary iron intake, lower meal frequency, lower dietary diversity, meal skipping, and snacking; menstruation: excessive bleeding[1] and menarche. [1] indicates majority.

included in this review. Five studies indicated that worm infestation significantly increased the odds of anaemia incidence in adolescents [40–44]. One cross-sectional study reported that malaria significantly increased the odds of anaemia in adolescents (OR = 3.68, 95% CI: 1.69–7.98) [41].

3.7. Female Adolescents. Eight studies reported on the relationship between female adolescents and anaemia [31, 32, 35, 37–41]. The studies showed significant and higher odds of female adolescents having anaemia. Four out of eight studies showed that older adolescents had higher odds of anaemia [35, 37, 38, 41].

3.8. Blood Loss/Menstruation. Five studies [31, 38, 42–44] assessed the relationship between anaemia and menstruation. Three out of five studies indicated that excessive bleeding during menstruation significantly increased the odds of anaemia [31, 43, 44]. According to Fentie et al. [31], adolescent girls who bleed for more than 5 days have an increased risk (AOR = 2.25, 95% CI: 1.17–4.33) of being anaemic. Regasa and Haidar [38] reported menstruation to be a statistically significant risk factor for anaemia in adolescents. However, Ramzi et al. [42] found no significant association between menstruation and anaemia in adolescents.

3.9. Educational Status. Among the four studies that reported on educational status as a risk factor of anaemia, three studies indicated that maternal education was a key determinant [32, 39, 45]. El Sahn et al. [45]; reported that the risk of anaemia increased significantly with decreased level of education (OR = 3.5, 95% CI: 10.90–6.32). Adolescents with education up to the junior high school level or lower were found to have increased odds of being anaemic [32, 33].

3.10. Socioeconomic Status. Three studies assessed the relationship between socioeconomic status and anaemia. The outcome indicated that low socioeconomic status increased the odds of anaemia in adolescents [31, 39, 45]. All studies found adolescents with low socioeconomic backgrounds to have increased odds of being anaemic, OR = 2.16, 95% CI: 1.17–4.33; OR 2.86, 95% CI: 1.16–7.04; OR = 1.4, 95% CI: 1.13–1.8; Fentie et al. [31]; Agrawal et al. [39]; and El Sahn et al. [45], respectively.

3.11. Rural Areas. Two studies reported on rural areas and anaemia [36, 38]. The studies showed that adolescents living in rural areas had an increased risk of anaemia. Regasa and Haidar found that the odds were statistically significant.

3.12. Family Size. Two studies assessed the relationship between family size and anaemia [36, 42]. The studies indicated that large family size increased the odds of anaemia. Ramzi et al. [42] showed significant association, while Shaka and Wondimagegne [36] indicated otherwise.

3.13. Religion. Only one study investigated the association between religion and anaemia. However, the results of the study showed no significant effects of religion on anaemia among adolescents [39].

3.14. Walking Barefooted. Only one study reported that adolescents who walk barefooted have higher odds of having anaemia [35]. According to the authors, adolescents who walked barefoot had a 1.78 chance of being anaemic (AOR = 1.78, 95% CI: 1.08, 2.94).

4. Discussion

The prevalence of anaemia among adolescents is of public health concern despite the application of varied interventions. Management and prevention of iron deficiency anaemia are complex, indicating that different factors contribute to IDA in different geographical settings. The

present study assessed the risk of iron deficiency anaemia among adolescents in developing countries. The risk factors of iron deficiency anaemia among adolescents are conglomerate. However, food intake practices, low educational status, parasitic infections, older adolescent girls, menstruation, and low socioeconomic status were the leading risk factors that predispose adolescents to iron deficiency anaemia (Figure 2).

4.1. Food Intake Practices. Adolescents prefer to explore their dietary environment and, thus, consume foods that are pleasing to the eyes with little or no consideration of the nutrients needed for their growth and well-being. Most adolescents binge on junk foods due to the neglect of a nutritious diet [47]. These poor food choices affect their nutrient needs, leading to micronutrient deficiencies, particularly anaemia. The negative effects of IDA on learning, scholastic performance, and achievement among adolescents contribute to dropout rates [21, 23, 25]. Adolescents with low educational status are unable to gain employable skills, thereby affecting their economic status [48]. Unskilled labour pays less as guardians are unable to give their children a good education and also meet their nutritional needs. These adolescents also become mothers of children with iron deficiency anaemia to perpetuate the cycle of consequences of anaemia. In this review, most of the studies found that vegetarian dietary practices increased the risk of anaemia among adolescents [39, 40, 43]. Inadequate dietary iron intake [41, 43] and low dietary diversity [31, 32] were second in contributing to IDA among adolescents. Most iron-rich food sources are expensive in developing countries [49]. Other food intake practices, such as meal skipping, lower meal frequency, lower dietary diversity, household food insecurity, and snacking, also increased the risk of IDA among adolescents. Poor nutrition has been a major risk factor for IDA among adolescents [40, 50].

4.2. Adolescent Girls. Our review showed that female adolescents had a higher risk of iron deficiency anaemia, particularly older girls. It was thus not surprising that eight of the fifteen studies focused on female adolescents [31, 34, 37, 38, 41–44]. Older girls may prefer to eat out of home, skip meals, and diet to maintain certain body curvature, making them more vulnerable to IDA. Most guardians have less control over an older adolescent girl's food intake. The fear of gaining weight and low nutrition knowledge influence the eating habits of adolescents and contribute to IDA [51, 52]. Menstruation and childbearing have increased the odds of anaemia in older adolescents. A nationwide study in Namibia, Malawi, Zimbabwe, and Mozambique showed that anaemic mothers have higher odds of delivering children with low haemoglobin levels [53].

4.3. Worm Infestation. The prevalence of worm infestations is estimated to be about 1.5 billion, with the majority of the population from sub-Saharan Africa, the Americas, China, and East Asia [54]. Roundworm (*Ascaris lumbricoides*), whipworm (Trichuris trichiura), hookworm (Necator americanus and Ancylostoma duodenale), and other helminths have been implicated in anaemia by causing gastrointestinal blood loss, poor nutrient absorption, inhibition or suppression of appetite, and general inflammation among adolescents [40, 54–56].

4.4. Guardian Education. Low educational status of guardians, particularly mothers, has been linked to a high risk of anaemia in adolescents in diverse settings and studies [32, 39, 57]. Mothers with limited formal education may not be able to read and understand food labels. Knowledge levels of nutrition by mothers are critical as most are key kitchen persons in most homes influencing food preparation, dietary choices, and intake of the family. Maternal education status has been shown to influence children's normal haemoglobin levels [58]. The education level of fathers and adolescents rarely led to iron deficiency anaemia within our target group.

4.5. Socioeconomic Status. Higher maternal education and employment status reduce the odds of iron deficiency anaemia in children [59]. Guardians with low educational status have low skilled employment with poor remuneration [60]. Low socioeconomic status due to unemployment affects the purchasing power of the household. Adolescents largely depend on guardians or parents for their financial and dietary needs. Households with low socioeconomic status face the risk of food insecurity, low dietary diversity, and inadequate food intake, which pose health risks [61, 62].

4.6. Strength and Limitations. The study gives an overview of the risk factors of iron deficiency anaemia among adolescents in developing countries. The sample sizes of most of the studies were not nationally representative, and female adolescents were the target for most of the studies; therefore, the outcome cannot be generalized.

5. Conclusion and Further Directions

The review showed that food intake practices, parasitic infections, menstruation, increasing age of female adolescents, and low educational status of guardians were the leading risk factors of iron deficiency anaemia among adolescents in most developing countries. Funding agencies should support nationally representative nutrition research to continue to identify localized risk factors that precipitate IDA among adolescents. Further studies should focus on assessing the effectiveness and efficacy of already existing interventions such as iron-folic acid supplementation, nutrition education, use of insecticide mosquito nets, and intermittent deworming of adolescents, and developing appropriate policies and programmes to strenghten such interventions. Developing countries should continue to adopt policies and programmes to sustain girl child education, maternal education, and economic empowerment of guardians, particularly women, to reduce the prevalence and

menace of IDA in adolescents. Governments and non-governmental organizations should prioritize adolescent nutrition as it is another gateway to having a positive impact on the lifecycle.

Data Availability

The data supporting this systematic review are from previously reported studies and datasets, which have been cited. The processed data can be obtained from the corresponding author upon reasonable request.

Ethical Approval

Findings of the study were in the public domain; therefore, the authors needed no ethical approval for the systematic review.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Michael Akenteng Wiafe conceptualized, designed, performed the original search, and drafted the manuscript. Jessica Ayensu conceptualized, designed, provided input, and reviewed the manuscript, and Divine Eli-Cophie designed, provided input, and reviewed manuscript. All authors have read and approved the manuscript.

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