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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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ABSTRAK (ENGLISH)

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.

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DETAIL

Subjek:	Anemia; Socioeconomic factors; Blood tests; Food; Blood transfusions; Body mass index; Age; Sickle cell disease; Sociodemographics; Gallbladder diseases; Bile ducts; Gallstones; Children &youth; Abdomen; Ultrasonic imaging; Hospitalization
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Preterm Delivery and Neonatal Deaths among Anaemic Pregnant Women in the Bolgatanga Metropolis of Ghana

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ABSTRAK (ENGLISH)

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.

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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.

[figure(s) omitted; refer to PDF]

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:(1)samplesizen o=z2pqe2,where,z=1.96,p=0.530,q=1−0.530=0.467,e=0.05,where z = confidence interval; e = margin of error; no = sample size; and p = prevalence of anaemia of the study population at 53.0%, i.e., 0.530:(2)no=1.96x1.960.5301−0.5300.05x0.05,no=3.84160.24750.0025,samplesizeno=380.

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

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.

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

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.

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%, *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).

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

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

3.3. Comparison of Socioeconomic, Clinical, and Obstetric Outcomes between Mothers with Preterm and Normal Delivery

No age differences were observed between 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.

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**

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.

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).

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

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.

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.

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.

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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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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ABSTRAK (ENGLISH)

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.

TEKS LENGKAP

DETAIL

Subjek:	Antigens; Blood transfusions; Antibodies; Blood diseases; Blood groups; Genotype &phenotype; Sickle cell disease; Sociodemographics
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A Case-Control Study of the Factors Associated with Anemia in Chinese Children Aged 3–7 years Old

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ABSTRAK (ENGLISH)

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.

TEKS LENGKAP

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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).

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)

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, 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).

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)
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)		
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)		

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).

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)

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 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.

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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Glossary

Abbreviations

OR:Odds ratio

CI:Confidence interval

G6PD:Glucose-6-phosphate dehydrogenase.

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DETAIL

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

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ABSTRAK (ENGLISH)

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.

TEKS LENGKAP

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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.

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
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.

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.

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.

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).

[figure(s) omitted; refer to PDF]

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” 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).

[figure(s) omitted; refer to PDF]

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 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.

Ethical Approval

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

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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The Prevalence and Pattern of Anaemia in Type 2 Diabetics in Ogbomosho, An Urban Community in Southwestern Nigeria

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ABSTRAK (ENGLISH)

Anaemia is a frequent finding in type 2 diabetes, but it is typically seen with established chronic kidney disease and renal insufficiency. Cases, where anaemia predates renal insufficiency, are associated with a worse prognosis for the type 2 diabetes patient and an increased susceptibility to complications. This study aims to determine the prevalence and type of anaemia in persons living with type 2 diabetes without established chronic kidney disease in our environment. The study was a hospital-based cross-sectional study that involved 141 people with known type 2 diabetes as the study group and 140 healthy persons as controls. The study population and the controls were selected using a multistage sampling technique. Data were collected using an interviewer-administered semistructured questionnaire at the Endocrinology clinic, Bowen University Teaching Hospital, Ogbomosho. The data obtained were analyzed using the IBM SPSS version 23.0 (p value ≤0.05 was considered significant). The biochemical (fasting lipids, HBA1C, FBG, serum albumin, creatinine, urea, uric acid, and insulin) and haematological (FBC and red cell indices; PVC, MCV, MCH, MCHC, and RCDW) parameters of the respondents were analyzed using standard methods. The study showed a statistically significant difference in the prevalence of anaemia among subjects, 69.2% as compared to 30.8% of the control group. Normochromic normocytic anaemia was predominant among the subjects, whereas microcytic hypochromic anaemia was the predominant type in the controls. There was no statistically significant difference between MCV and MCHC of both subjects and controls. There was a positive correlation between the incidence of anaemia and the duration of diabetes among the subjects. More people with type 2 diabetes are now living longer, and the addition of haematological parameters should be part of their baseline investigations to aid in the early detection of complications.

TEKS LENGKAP

DETAIL

Subjek:	Software; Insulin resistance; Diabetes; Plasma; Sampling techniques; Body mass index; Kidney diseases; Gender; Skilled workers; Fluorides; Ethnicity; Ethics; Patients; Sample size; Hemoglobin; Anemia; Blood tests; Age; Blood pressure; Health care; Endocrinology; Sociodemographics; Glucose; Education; Teaching hospitals
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Burden and Determinants of Anemia among Under-Five Children in Africa: Systematic Review and Meta-Analysis

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ABSTRAK (ENGLISH)

Introduction. Globally, anemia among under-five children is a serious public health problem. Even if there are pocket studies here and there, there is limited evidence on the pooled prevalence of anemia among under-five children in Africa. Therefore, the aim of this study was to determine the pooled prevalence and determinants of anemia. *Methods and Analysis*. This systematic review and meta-analysis was done following the PRISMA guidelines. A comprehensive search was made in PubMed/MEDLINE, Cochrane Library, HINARI, and Ethiopian Journal of Health

Development for studies published since 2009. It was supplemented with Google Scholar search. Study selection, data extraction, and quality of studies were assessed by eight reviewers. The Cochrane Q test and I^2 test statistic were used to test the heterogeneity of studies. A random-effects model of DerSimonian-Laird method was used. *Result*. A total of 37 articles were included in this systematic review and meta-analysis. The pooled prevalence of anemia among under-five children in Africa was 59% (95% CI: 55, 63). Being female (AOR = 0.71; 95% CI: 0.57, 0.87), maternal education (AOR = 1.47; 95% CI: 1.31, 1.66), residence (AOR = 0.80; 95% CI: 0.67, 0.95), and family size (AOR = 0.93; 95% CI: 0.89, 0.98) were the determinants of anemia among African under-five children. *Conclusion and Recommendation*. This pooled study revealed that anemia was a severe public health problem. Sex, maternal education, residence, and family size were the determinants of anemia. Therefore, anemia prevention strategy should include sex consideration, educating mothers through youth education, area specific intervention, and encouraging birth spacing.

TEKS LENGKAP

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1. Background

Anemia among under-five children is defined as a hemoglobin level <11 mg/dl or children with hematocrit less than 33% [1]. Worldwide, anemia among under-five children is a major public health problem [2]. Globally, 20 million infants were born with low birth weight (LBW) every year. Nearly, 3.6 million of them died before celebrating their 28 days, of whom almost two-thirds were located in Sub-Saharan Africa and Southern Asia [3]. The effect of anemia can extend up to postpartum period and even newly delivered baby may suffer from a reduced iron store problem up to one year [4]. In developing countries, 46–66% of children under the age of five were affected by anemia [3]. African and Asian regions were the major contributor for a high burden of anemia [5].

The rapid growth and cognitive development of children make them more vulnerable for the development of anemia [6]. The consequences of iron deficiency anemia (IDA) during childhood include growth retardation, reduced school achievement, impaired motor and cognitive development, and increased morbidity and mortality. Mental impairments at early age are thought to be irreversible and the consequences may continue even after treatment, reinforcing the importance of early detection and prevention [7, 8].

The causes for anemia among under-five children are complex. Among these, low birth weight, undernutrition, poor socioeconomic status, household food insecurity, duration of breast feeding, poor dietary iron intake, poor maternal educational status, diarrhea, fever, poverty, poor sanitation and hygiene, monotonous diet, parent’s level of education, and maternal anemia were the commonest contributors for under-five anemia [9–13].

Despite the numerous interventions done so far by the government of African countries and other concerning stakeholders, anemia among under-five children is still a severe public health concern [14–19]. Even though many independent pocket studies have been conducted in the region, the results were inconsistent and the prevalence varies significantly between studies [20–22]. In Africa, the pooled prevalence and determinants of anemia among under-five children have not been yet done. Assessing the pooled result will help to inspire the government’s commitment and increase the social and resource mobilization in order to enhance the implementation of evidence based interventions for culminating the effect of anemia among under-five children in particular and the nation in general. Therefore, the aim of this study was to determine the pooled prevalence and determinants of anemia among under-five children in Africa. The findings of this study will help policy makers, program planners, health care providers, and concerned stakeholders to work more on anemia in order to reduce the prevalence of anemia, its consequences, and complication among under-five children.

Prompt identification and treatment of anemia lead to overall improvement of population health outcomes, improved physical exercise performance, and well-being that results in enhanced economic productivity.

2. Methods and Materials

2.1. Patient and Public Involvement

All under-five children in Africa were involved in this study.

2.2. Eligibility Criteria

All studies that reported prevalence and determinants of anemia among under-five children in Africa using English language and gray literatures were included. For estimating the prevalence of anemia, studies with cross-sectional design were included, while, for pooling the determinants of anemia, cross-sectional and case-control studies were included in the study. While studies whose full texts cannot be accessed after trying to contact the primary investigator within 3 months, descriptive studies, systematic reviews of the effects of an intervention, review articles, conference abstract and editorials were excluded from the study.

2.3. Search Strategies

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [23]. The study was conducted following the Joanna Briggs Institute (JBI) criteria. Data bases such as MEDLINE (via PubMed), EMBASE, and Cochrane Library, SCOPUS, HINARY, and Google Scholar were used to extensively search the relevant articles conducted since January 1, 2009. Gray literatures were also included by manual search.

2.4. Search Terms Used

The strategy applied to search articles from the electronic data bases was (anemia) OR ("iron deficiency anemia") OR ("low hemoglobin level") AND (determinants) OR ("associated factors") ("Under Five Children") AND (Ethiopia) OR (Eritrea) OR (Kenya) OR (Angola) OR (Benin) OR (Botswana) OR ("Burkina Faso") OR (Burundi) OR (Cameroon) OR ("Cape Verde") OR ("Central African Republic of Chad") OR (Comoros) OR (Congo) OR ("Côte d'Ivoire") OR (Djibouti) OR ("Equatorial Guinea") OR (Gabon) OR (Gambia) OR (Ghana) OR (Guinea) OR ("Guinea-Bissau") OR (Lesotho) OR (Liberia) OR (Madagascar) OR (Malawi) OR (MAli) OR (Mauritania) OR (Mauritius) OR (Mozambique) OR (Namibia) OR (Niger) OR (Nigeria) OR (Réunion) OR (Rwanda) OR ("Sao Tome and Principe") OR (Senegal) OR ("Seychelles") OR (Sierra Leone) OR (Somalia) OR ("South Africa") OR ("Sudan") OR (Swaziland) OR (Tanzania) OR (Togo) OR (Uganda) OR ("Western Sahara") OR (Zambia) OR (Zimbabwe).

2.5. Data Extraction

After obtaining the full text of all articles, duplicates were screened and removed from the citation manger. Based on the eligibility criteria, eight reviewers (SE, AA, TC, AW, MY, FM, FY, and YW) independently reviewed the studies by title, abstract, and full article. Those included and undecided studies were further assessed by reading the full text. Studies that were not eligible based on the full text assessment were excluded and reasons were described for their exclusion in combination with the PRISMA flow diagram to summarize the selection procedure [23]. Studies that passed through this selection process were included in this study. Discrepancies between authors were resolved through discussion and consensus. The study characteristics (author, year of publication, region, target group, sample size, study design, response rate, and children with anemia), subject recruitment procedures, count data with (2 × 2 tables), crude odds ratio (where count data were not found), and population characteristics were extracted by using extraction sheet developed with Microsoft Excel 2013.

2.6. Quality Assessment and Risk of Bias

The Joanna Briggs Institute (JBI) critical appraisal check list was used to assess the quality of each paper. During data extraction, eight investigators independently performed the quality assessment. The quality scores of six data extractors were averaged. Any disagreement between investigators was solved by discussion and consensus. Finally, studies with higher scores (>50%) were included in the systematic review and meta-analysis.

2.7. Data Synthesis and Analysis

Data were analyzed using STATA version 14.0. The pooled proportion was calculated to estimate the prevalence of anemia. The pooled odds ratio (OR) with 95% CI was determined to estimate the determinants of anemia among under-five children. The degree of heterogeneity was checked by Cochran Q and I^2 statistics. The Cochrane Q statistic was considered significant, if the Pvalue is <0.10, while the I^2 statistics at least 50% was considered to be significant [24, 25]. Since the variation between the study findings is significant, a random-effects model with 95% confidence interval was used. Heterogeneity was checked by running metaregression, subgroup analysis, and sensitivity analysis. Subgroup analysis was performed based on sex and study setting (region). Funnel plots

analysis, Egger weighted regression, and Begg rank correlation tests were done to detect publication bias ($P<0.05$ was considered as a suggestive of statistically significant publication bias) [25, 26].

2.8. Registration and Reporting

This systematic review and meta-analysis was registered in the PROSPERO with a CRD number of 42020150881.

2.9. Ethical Clearance

This study was reviewed and approved by institutional review board of College of Medicine and Health Sciences, Wollo University.

3. Result

A total of 331,236 articles were retrieved by literature search (Figure 1). Of these, 129,180 were excluded because of duplication, 201,898 did not have any relation with the aim of this study, and 121 did not meet the eligibility criteria. Finally, only 37 articles were included in this systematic review and meta-analysis. All included articles were full text and done using cross-sectional study design with one cohort [27] and three case controls [28–30]. The sample population varied from 210 [28] to 8,260 [31] children aging between 0 and 59 months. In this study, a total of 67,647 under-five children were included. The overall information regarding the prevalence of anemia was obtained from twenty African countries. These countries were Benin [32], Cameroon [33], Cape Verde [34], Congo [22], Ethiopia [14, 15, 31, 35–42], Gambia [43], Ghana [18, 28, 44], Guinea [20, 45], Kenya [19, 46], Lesotho [47], Malawi [48], Mozambique [29], Nigeria [49, 50], Rwanda [21], Senegal [17], Sierra Leone [51], South Africa [27], Tanzania [16, 30, 52–55], Togo [56], and Uganda [57–59] (Table 1).

[figure(s) omitted; refer to PDF]

Table 1

Summary of extracted studies on anemia among under-five children in Africa, 2009–2020.

Author	Publication year	Study setting	Target group	Study design	Sample size	Prevalence	Quality
Gaston et al.	2009	Lesotho	Under five	Cross-sectional	1295	49	76.5
Gaston et al.	2014	Lesotho	Under five	Cross-sectional	1139	54	76.5
Guled and Mamat	2017	Ethiopia	6–59 months	Cross-sectional	397	72.0	67
Amugsi	2019	Ghana	6–59 months	Cross-sectional	2451	68.0	88
Woodruff et al.	2018	Guinea	Under five	Cross-sectional	5681	34	79
G/Egziabiher et al.	2014	Ethiopia	6–59 months	Cross-sectional	568	37	70.57
Simbauranga et al.	2015	Tanzania	Under five	Cross-sectional	448	77	58.9

Muchie	2016	Ethiopia	6–59 months	Cross-sectional	7636	50	61.8
Melako et al.	2019	Ethiopia	6–23 months	Cross-sectional	477	52.0	66.5
Kateera et al.	2015	Rwanda	6–59 months	Cross-sectional	1882	7.0	75.55
Melku et al.	2018	Ethiopia	6–59 months	Cross-sectional	707	29	80.3
Thorne	2013	Guinea	6–59 months	Cross-sectional	872	82.0	64.3
Diouf et al.	2013	Senegal	9–15 months	Cross-sectional	245	87	73.5
Woldie et al.	2015	Ethiopia	6–23 months	Cross-sectional	346	66	56.4
Van Buskirk et al.	2014	Ghana	0–36 months	Cross-sectional	861	83	61.5
Ntenda et al.	2017	Malawi	6–59 months	Cross-sectional	2597	63	67.8
Gebreweld et al.	2019	Ethiopia	6–59 months	Cross-sectional	404	41	65.9
Wasihun et al.	2020	Ethiopia	6–9 months	Cross-sectional	610	58	68.8
Mghanga et al.	2017	Tanzania	0–59 months	Cross-sectional	303	83	74
Habte et al.	2013	Ethiopia	6–59 months	Cross-sectional	8260	50	57.5
Ali	2018	Uganda	Under five	Cross-sectional	1808	50	66.5
Petry et al.	2019	Gambia	Under five	Cross-sectional	1354	50	78.4

Ojoniyi et al.	2019	Tanzania	Under five	Cross-sectional	7916	58	82.1
Kejo et al.	2018	Tanzania	6–59 months	Cross-sectional	436	85	67.5
Wirth et al.	2016	Sierra Leone	Under five	Cross-sectional	710	76	64.3
Kuziga et al.	2017	Uganda	6–59 months	Cross-sectional	376	59	52.9
Nambiema et al.	2019	Togo	6–59 months	Cross-sectional	2890	63	55.6
Semedo et al.	2014	Cape Verde	6–59 months	Cross-sectional	993	52	60.8
Alaofè et al.	2017	Benin	6–59 months	Cross-sectional	681	82	53.5
Roba et al.	2013	Ethiopia	6–23 months	Cross-sectional	216	54	72.1
Jemal et al.	2016	Ethiopia	6–59 months	Cross-sectional	399	52	66
Bahizire et al.	2017	Congo	6–59 months	Cross-sectional	838	47	71
Foote et al.	2013	Kenya	6–35 months	Cross-sectional	858	72	79
Wangusi et al.	2016	Kenya	6–23 months	Cross-sectional	227	76	68.1
Menon and Yoon	2015	Uganda	Under five	Cross-sectional	3878	61	80.1
Ojoniyi O	2017	Tanzania	Under five	Cross-sectional	6592	57	84
Engle-Stone et al.	2017	Cameroon	12–59 months	Cross-sectional	291	45	63.3
Total sample size					69,253	59.0	

3.1. Prevalence of Anemia among Under-Five Children in Africa

The overall pooled prevalence of anemia among under-five children in Africa was 59% (95% CI: 55, 63). The true variability among studies other than chance was 100% (I^2 = 100%, Pvalue = 0.000). The lowest prevalence was observed in Rwanda 7% (95% CI: 7%, 7%), while the highest prevalence was observed in Senegal 87% (95% CI: 86%, 87%) (Figure 1). A study done in Rwanda did not include the milder form of anemia. This may be the reason for the lowest report of anemia prevalence in Rwanda (Figure 2).

[figure(s) omitted; refer to PDF]

To deal with the possible sources of heterogeneity, subgroup analysis was done by sex and region (study setting). The analysis result showed that heterogeneity still exists in both parameters mentioned above. In terms of region, the sources of heterogeneity were Ethiopia, Tanzania, Lesotho, Ghana, and Uganda.

The following funnel plot appears asymmetric; even if it indicates the presence of publication bias, it was not statistically significant (Figure 3).

[figure(s) omitted; refer to PDF]

3.2. Sensitivity Analysis

3.2.1. Determinants of Anemia among Under-Five Children in Africa

The result of this systematic review and meta-analysis indicated that sex of a child, maternal educational status, residence, and family size were the pooled determinants of anemia among under-five children in Africa. Being female is a protective against anemia among under-five children (AOR = 0.71; 95% CI: 0.57, 0.87), Mothers who were unable to read and write were 53% times more likely to have anemic child (AOR = 1.47; 95% CI: 1.31, 1.65). Those children from rural setting were 20% less likely to be affected by anemia as compared to children from urban setting (AOR = 0.80; 95% CI: 0.67, 0.95). Under-five children from a family size of less than five were 7% less likely to be affected by anemia (AOR = 0.93; 95% CI: 0.89, 0.98) (Table 2).

Table 2

Pooled determinants of anemia among under-five children in Africa, 2009–2020.

Variables		Pooled AOR (95% CI)	Heterogeneity			Pvalue
I^2	Q statistic	Pvalue	Malaria falciparum	Yes	1.31 (0.85, 1.78)	95.5%
15.74	0.000	0.22	No	1		
		-				
Sex	Female	0.71 (0.57, 0.87)	94.1	240.3	0.000	0.001
Male	1					
Stunting	Yes	1.16 (0.94, 1.43)	0.00	2.79	0.99	0.17
No	1					
Maternal education	Informal	1.47 (1.31, 1.65)	0.00	5.69	0.89	0.00

Elementary	1.05 (0.89, 1.25)	0.0	2.00	0.99	0.62	High school
1						
Diarrhea	Yes	1.44 (0.86, 2.42)	93.9	245.06	0.00	0.17
No	1					
ANC follow-up	Yes	1.68 (0.46, 6.23)	0.0	0.08	0.43	0.43
No	1					
Residence	Rural	0.80 (0.67, 0.95)	0.0	5.14	0.64	0.000
Urban	1					
IFA intake	Yes	0.99 (0.63, 1.57)	0.0	0.00	0.73	0.44
No	1					
Family size	<5	0.93 (0.89, 0.98)	0.0	4.19	0.52	0.004
≥5	1					
Occupation	Unemployed	1.14 (0.86, 1.51)	0.0	1.77	0.98	0.38

4. Discussion

This study was aimed at estimating the pooled prevalence and determinants of anemia among under-five children in Africa by reviewing the existing pocket studies. Based on the finding of this study, the pooled prevalence of anemia among under-five children in Africa was 59%. This finding is in line with a global prevalence of anemia [60]. According to the classification of World Health Organization (WHO), it was categorized under severe public health problem [61]. This finding suggests that, based on the current pace, it is difficult to achieve the global 50% reduction of anemia by 2025 in Africa [62].

This study showed that sex was a significant predictor of anemia among under-five children. Being female is protective against anemia among under-five children. The possible explanation for anemia discrepancy by sex could be due to the state of rapid growth of male children compared to females in the first months of life which increases their micronutrient requirement including iron, which cannot be met by diet alone [63]. If this physiological state is not compensated with iron rich complementary foods, risk of iron deficiency anemia will be higher in male children as compared to females.

This finding revealed that maternal education was a significant predictor of anemia among under-five children. Mothers with informal education were 53% more likely to have child with anemia. This finding is in line with a systematic review and meta-analysis study conducted in Ethiopia [64]. This might be because mothers with no formal education may not understand the introduction of scientifically sound feeding practices and are less likely to follow the recommended child feeding practices [65]. In addition, mothers with no education were negatively affecting the socioeconomic status of households which in turn limits food purchasing power and is a strong

predictor for nutritional outcomes of children. Hence, their access to hem iron source food is limited [66]. In order to tackle the effect of anemia in children, nutrition education is suggested for mothers [67].

This study indicated that residence was a significant predictor of anemia among under-five children. Those children from rural setting were 20% less likely to be affected by anemia as compared to children from urban setting. This may be because mothers in the rural setting will breastfed their children exclusively till six months of age and continue breastfeeding till 24 months and more. Since iron in breast milk is more likely to be absorbed and utilized by the child's body, it will contribute for the normal stores of iron, which will help in reducing anemia among under-five children. In order to turn on the health loss due to anemia in children, UNICEF and WHO jointly recommended adequate breastfeeding practices [67]. But the finding of this study is inconsistent with a systematic review and meta-analysis study conducted in Ethiopia [64].

This study showed that family size was a significant predictor of anemia among under-five children in Africa. Those children from a household size of <5 were 7% less likely to be anemic as compared to their counterparts. This could be because large family size is associated with food insecurity. The lesser the families are, the more likely adequate and diversified diet can be afforded, which is rich in iron [68].

Some of the limitations of this study were articles published only in English language that were included. This may affect the prevalence estimation of anemia. Another limitation of this study was articles which were conducted among pediatrics that were not included. The data were obtained from twenty African countries. However, the analyzed pooled prevalence may not fully represent the prevalence of anemia in Africa because there is lack of evidences in some parts of the region.

To conclude, based on this systematic review and meta-analysis, anemia was a severe public health problem among under-five children in Africa. Sex, maternal education, residence, and family size were the determinants of anemia among under-five children. Therefore, adequate intervention should be designed by considering sex and residence difference, addressing maternal illiteracy through youth education and nutrition education, and promoting birth spacing.

Authors' Contributions

SE and AA participated in the conceptualization, searching, and selection, data extraction and analysis, writing, and approving the manuscript. TC participated in data extraction and analysis, report writing-up, writing, and approving the manuscript. AW and FY participated in the conceptualization, searching, and selection, writing, and approving the manuscript. FM participated in the conceptualization, editing, and approving the manuscript. MY took part in searching and selection, data analysis, revising, and approving the manuscript. YW contributed to searching and selection, data extraction and analysis, writing the manuscript, and approving the manuscript.

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DETAIL

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Molecular Characterization and Genotype-Phenotype Correlation of G6PD Mutations in Five Ethnicities of Northern Vietnam

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ABSTRAK (ENGLISH)

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme disorder and is caused by G6PD gene mutations. To date, more than 400 variants in the G6PD gene have been discovered, and about 160 identified variants are associated with a significant decrease in the G6PD enzyme activity. However, the molecular characterization and epidemiological study of G6PD deficiency are still limited in Vietnam. Therefore, we conducted this study to determine the G6PD variants among the Vietnamese populations and evaluate their correlation to G6PD enzyme activity. A total of 339 patients (302 males and 37 females) were enrolled in this study. The G6PD variants were identified by Sanger sequencing. Our results indicate that males are more severely deficient in G6PD than females. This enzyme activity in males (1.27 ± 1.06 IU/g·Hb) is significantly lower than in females (2.98 ± 1.57 IU/g·Hb) ($p<0.0001$). The enzyme activity of the heterozygous-homozygous females and heterozygous females-hemizygous males was found to be significantly different ($p<0.05$), which is interpreted due to random X-inactivation. For G6PD molecular characteristics, *Viangchan* (c.871G>A), *Canton* (c.1376G>T) and *Kaiping* (c.1388G>A) variants were the most dominant, accounting for 24.48%, 17.70%, and 22.42%, respectively, whereas the highest frequency of complex variants was observed in *Viangchan/Silent* with 20.35%. In terms of G6PD activity, the *Union* variant presented the lowest mean value (1.03 IU/g·Hb) compared to the other variants ($p<0.05$). Computational analysis using Polyphen-2 tool investigated that all variants were relative to G6PD deficiency and separated the levels as benign and damaged. The result will establish effective methods to screen G6PD variants in Vietnam.

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1. Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is a key cytosolic enzyme in the pentose phosphate pathway (PPP) to produce NADPH which plays an important role in protecting the red blood cells from oxidative stress by reducing glutathione dimers oxidized and sulfhydryl groups [1]. The lack of the G6PD enzyme can cause hemolytic and related disorders such as clinical acute hemolysis, neonatal jaundice, and congenital hemolytic anemia [2,3]. G6PD deficiency, also known as favism, is the most prevalent enzyme disorder and is found worldwide [4–6]. An estimated 400 million people were influenced globally by G6PD, and an average of 4100 people died every year from 1990 to 2013 [7]. Based on the residual enzyme activity and clinical manifestations, G6PD deficiency is categorized into five groups by the WHO. Class I (less than 1% of normal activity) has been considered the most serious among classes and is specifically associated with chronic nonspherocytic hemolytic anemia (CNSHA). Class II (1 to 10% of normal) is highly associated with acute hemolytic anemia, while Class III (10 to 60% of normal) is normally associated with occasional acute hemolytic anemia, and Class IV (60 to 150% of normal) and Class V (>150% of normal) are mostly asymptomatic [8].

G6PD is encoded by the G6PD gene which is located in the telomeric region of the X chromosome (Xq28). Thus, G6PD deficiency has been inherited as the X-linked incomplete dominant. While males are always hemizygous because of having only one X chromosome, females with this disorder may be heterozygous or homozygous and have less severe clinical manifestations [9]. The G6PD gene is 18.5 kb in size with 13 exons and codes for 515 amino acids of the G6PD enzyme. To date, more than 400 variants in the G6PD gene have been discovered, and about 160 identified variants show a significant decrease of the enzyme in erythrocytes [10,11]. The vast majority of G6PD variants are single-base substitutions and are distributed as follows: 85.4% are missense, 8% are multiple mutations, 5.3% are deletions, and 1% are mutations within introns [12]. Moreover, many variants present genetic characteristics within specific populations, geographic regions, and ethnic groups [13]. For example, the *G6PD Mediterranean* (c.563C>T) variant is widely distributed in Southern Europe, the G6PD A-variant is predominant in African origins, and the G6PD *Mahidol* (c.487G>A) and *Viangchan* (c.871G>A) variants are mostly associated with Asians, especially in Myanmar and Cambodian populations [14–16]. Furthermore, the correlation between these variants and the deficiency of the G6PD enzyme is being investigated. The G6PD variants such as *Canton* (c.1376G>T), *Kaiping* (c.1388G>A), and *Gaohe* (c.95A>G) have been identified to reduce enzyme activity by up to 90% in the Chinese population. Different variants can cause varying enzyme activities [17,18].

In Vietnam, G6PD deficiency is also a prevalent genetic disorder with an incidence rate of about 8.9% and a diverse distribution according to ethnic groups and regions [19,20]. Several G6PD variants are characterized by being detected in the Vietnamese population, such as *Vietnam1* (c.7G>A), *Vietnam2* (c.197T>G), and *BaoLoc* (c.352T>C) [21,22]. However, the correlation between specific G6PD variants and these activity genotypes has not been reported. Also, the molecular epidemiology of G6PD deficiency is still limited in Vietnam. To provide more information to diagnose this disorder, we performed this study to carry out the prevalence of G6PD deficiency and G6PD variants in the Vietnamese population by direct sequencing. These data will contribute to prenatal genetic counseling to reduce morbidity, reduce consequences for the patient's family and society, and improve the quality of health care in the community.

2. Materials and Methods

2.1. Sample Collection

To screen G6PD variants, 339 pediatric patients were selected from 25 provinces of Northern Vietnam and confirmed G6PD deficiency with an enzyme activity less than 6 IU/g·Hb by Vietnam National Children’s Hospital from 2017 to 2020. The patients belonged to five different ethnic groups: Kinh, Mong, Muong, Thai, and Tay. The ages were arranged between 1-month-old and 24-month-olds. The participants consented to enroll before the study´s commencement. Whole blood samples were obtained in K2-EDTA tubes with a concentration of 1.5 mg/mL, then the

G6PD enzyme activity was measured by an automated biochemistry analyzer AU5800/AU680 (Beckman Coulter, USA) at the Department of Biochemistry, Vietnam National Children's Hospital.

2.2. Molecular Characteristic Analysis of G6PD Variants

Genomic DNA was extracted from peripheral blood samples by following the Wizard Genomic DNA purification kit instruction (Promega, USA). The primers for amplifying the G6PD gene were designed according to Nguyen Thi Hue et al. (2009) with minor modifications [21]. For PCR, the mixture contains GoTaq Hot Start Master Mix (2X), primer set (1 μM), DNA template (50 ng/μL), and sterile water. The PCR conditions were performed by initial denaturation at 95°C for 2 min, followed by 35 cycles of denaturation at 95°C for 30 s, annealing at 60°C for 30 s, and extension at 72°C for 30 s, followed by a final extension at 72°C for 5 min then holding at 4°C. After purification, PCR amplicons were sequenced by an ABI 3500xl Genetic Analyzer (Applied Biosystems, France). To identify G6PD variants, the sequencing results were analyzed by CLC Main Workbench software and assembled with the G6PD sequence on GenBank (NG_009015).

2.3. Damaging In Silico Analysis

The estimated damage score was evaluated by using the PolyPhen-2 web server (genetics.bwh.harvard.edu/pph2/index.shtml) [23]. For PolyPhen-2, the predicted function of a variant is classified as benign, possibly damaging, or probably damaging, with the scale score arranged from 0 to 0.5, 0.5–0.9, and 0.9–1, respectively. The G6PD query protein sequence from UniProtKB (P11413) was mapped as a reference.

2.4. Statistical Analysis

Statistical analysis was evaluated by GraphPad Prism ver.9 software. Comparison among groups was conducted using one-way ANOVA. Variables such as age, detection rate, and genotype were described by descriptive statistics. A chi-square test was applied for the comparison of frequencies of G6PD deficiency between both genders. A pvalue

3. Results

3.1. Patient Clinical Characteristics

A total of 339 patients were enrolled in this study, which contained 302 males (89.09%) and 37 females (10.91%) from five different ethnicities: Kinh, Muong, Nung, Thai, and Tay. The participant characteristics are listed in Table 1. The infants' age was distributed from less than 1-month old (79.06%) to over 24-months old (0.88%). There was a significant difference in age between males and females (p=0.0089) (Table 1). The G6PD enzyme activity was measured as 1.46 ± 1.24 IU/g·Hb on average. A significant difference was valued between both genders with 1.27 ± 1.06 IU/g·Hb in males and 2.98 ± 1.57 IU/g·Hb in females (p<0.0001) (Figure 1(a)). In normal conditions, the G6PD reference range at 37°C is 6–20.5 IU/g·Hb. The level of G6PD deficiency was categorized as high level (<0.6 IU/g·Hb) with 79 patients (23.30%), medium level (0.6–3.6 IU/g·Hb) with 233 patients (68.74%), and low level (3.6–9 IU/g·Hb) presented in 27 patients (7.96%). There was a significant difference in these levels between genders (p< 0.0001). Among 339 cases, 332 cases were found to carry G6PD genetic variants in both males and females including homozygous (2.36%), hemizygous (85.84%), and heterozygous (8.55%) (p<0.0001). No G6PD variants were recorded in 11 cases (3.25% in males) (Table 1).

Table 1

Participant characteristics in this study.

	Male	Female	*Total*	*p*
Age				
<1 month	244 (71.98)	24 (7.08)	268 (79.06)	0.0089*
1–6months	50 (14.75)	9 (2.61)	59 (17.41)	

>6–12 months	5 (1.48)	1 (0.29)	6 (1.77)	
>12–24 months	1 (0.29)	2 (0.59)	3 (0.88)	
>24 months	2 (0.59)	1 (0.29)	3 (0.88)	
N	**302**	**37**	**339**	
–				
Enzyme activity (IU/g·Hb)				
Average	1.27 ± 1.06	2.98 ± 1.57		<0.0001*
–				
The G6PD deficiency level of participants				
High (<0.6 U/g·Hb)	78 (23.01)	1 (0.29)	79 (23.30)	<0.0001*
Medium (0.6–3.6 IU/g·Hb)	212 (62.54)	21 (6.20)	233 (68.74)	
Low (3.6–9 IU/g·Hb)	12 (3.54)	15 (4.42)	27 (7.96)	
N	**302**	**37**	**339**	
–				
Genotype				
No mutation	11 (3.25)	0	11 (3.25)	<0.0001*
Homozygous	0	8 (2.36)	8 (2.36)	
Hemizygous	291 (85.84)	0	291 (85.84)	
Heterozygous	0	29 (8.55)	29 (8.55)	
N	302	37	339	

[figure(s) omitted; refer to PDF]

3.2. Prevalence of the G6PD Enzyme Activity in Five Ethnic Groups

In our study, the five selected ethnicities were distributed in Northern Vietnam. The majority of samples were arranged in Kinh, followed by Muong, Tay, Nung, and Thai with different prevalences of 61.6%, 16.5%, 10.7%, 6.5%, and 4.7%, respectively (Figure 2(a)). Also, the Tay population presented the highest enzyme activity (1.61 ± 1.37 IU/g·Hb), and the lowest enzyme activity was observed in the Muong population (1.26 ± 1.16 IU/g·Hb) (Figure 2(b)). However, no significant difference was recorded between the enzyme activity and ethnic groups (p=0.6487).

[figure(s) omitted; refer to PDF]

3.3. Identification and Function Prediction of G6PD Variants

With 339 participants, 14 G6PD variants were detected by using the Sanger sequencing method and categorized into two types: missense and silent (Table 2) (Figure 3). Of these, the *Viangchan* (c.871G>A), *Canton* (c.1376G>T), and *Kaiping* (c.1388G>A) variants were the most dominant across the five ethnic groups, accounting for 24.48%, 17.70%, and 22.42%, respectively (Figures 3(h), 3(m), 3(n)). A silent variant (c.1311C>T) in exon 11 was also found with a high frequency (25.66%) (Figure 3(o)). Moreover, the *NanKang* (c.517T>G), *Mediterranean* (c.563C>T), *Coimbra Shunde* (c.592C>T), and *Taiwan-2* (c.1330G>A) variants were relatively rare and were only detected in one sample each (0.29%) (Figures 3(e), 3(f), 3(g), 3(j)). In addition, the coexistent variants were found in our samples with variable frequencies, mostly together with *Silent* variants (c.1311C>T), presented in *Valladolid/Silent* variant (0.59%), *Viangchan/Silent* variant (20.29%), *Union/Silent* variant (2.06%), *Canton/Silent* variant (0.59%), and *Kaiping/Silent* variant (0.88%) (Table 2). A unique variant between *Canton* and *Kaiping* was found in one tested individual (0.29%) (Figure 3(o)).

Table 2

Distribution of G6PD variants in this study.

Variant name	Position	Amino acid substitution	Type of variant	Exon	Case	Frequently (%)	In silico analysis
Gaohe	c.95A>G	H32A	Missense	2	24	7.08	Damaging score: 0.998
Orissa	c.131C>G	A44G	Missense	3	3	0.88	Damaging score: 991
Quing Yan	c.392G>T	G131V	Missense	5	12	3.54	Damaging score: 0.826
Valladolid	c.406C>T	L142C	Missense	5	2	0.59	Damaging score: 1
NanKang	c.517T>G	F173L	Missense	5	1	0.29	Damaging score: 1
Mediterranean	c.563C>T	S188P	Missense	5	1	0.29	Benign score: 0.371
Coimbra Shunde	c.592C>T	R198C	Missense	6	1	0.29	Damaging score: 1
Viangchan	c.871G>A	V291M	Missense	9	83	24.48	Damaging score: 0.996
Chinese-5	c.1024C>T	L342F	Missense	9	14	4.13	Benign score: 0.205

Taiwan-2	c.1330G>A	V444I	Missense	11	1	0.29	Benign score: 0.127
Union	c.1360C>T	R454C	Missense	11	51	15.04	Damaging score: 1
Canton	c.1376G>T	R459L	Missense	12	60	17.70	Damaging score: 0.910
Kaiping	c.1388G>A	R463H	Missense	12	76	22.42	Damaging score: 0.860
Silent	c.1311C>T	T437T	Silent	11	87	25.66	N/A
Valladolid/Silent	c.406C>T	A142C	Missense	5, 11	2	0.59	N/A
	c.1311C>T	T437T	/Silent				
Viangchan/Silent	c.871G>A	V291M	Missense	9, 12	69	20.35	N/A
	c.1311C>T	T437T	/Silent				
Union/Silent	c.1360C>T	R454C	Missense	11	7	2.06	N/A
	c.1311C>T	T437T	/Silent				
Canton/Silent	c.1376G>T	R459L	Missense	11, 12	2	0.59	N/A
	c.1311C>T	T437T	/Silent				
Kaiping/Silent	c.1388G>T	R463H	Missense	11, 12	3	0.88	N/A
	c.1311C>T	T437T	/Silent				
Canton/Kaiping	c.1376G>T c.1388G>A	R459L, R463H	Missense	12	1	0.29	N/A

[figure(s) omitted; refer to PDF]

PolyPhen-2 is a useful automatic tool for the prediction of the possible impact of an amino acid substitution on the structure and function of a human protein [23]. In this study, computational analysis was performed to estimate the risk of disease among G6PD variants. A total of 14 variants, four of them were identified to have the maximum damaging score (DS = 1) including *Valladolid*, *NanKang*, *Coimbra Shunde*, and *Union*, and the benign score was observed in *Mediterranean* (0.371), *Chinese-5* (0.205), and *Taiwan-2* (0.127) (Table 2). A high-risk score was also

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accessed in the remaining variants, arranging from 0.860 to 0.998. The *Silent* variant (c.1311C>T) did not give any score by Polyphen-2 because it was a silent variant.

3.4. Correlation between the Genotype and the G6PD Activity Phenotype

According to the WHO instruction, the 13 identified G6PD variants in our study were predominantly identified in Class II and III, except for the silent variant. Among these variants, *Gaohe*, *Orissa*, *Quing Yan*, *Chinese-5,* and *Taiwan-2* were categorized as Class III, while *Valladolid*, *NanKang*, *Mediterranean*, *Coimbra Shunde*, *Viangchan*, *Union*, *Canton*, and *Kaiping* were categorized as Class II (Table 3). The G6PD variant genotype was mainly found in hemizygous (294/332) males (1.26 ± 1.04 IU/g·Hb), while homozygous (8/332) and heterozygous genotypes (29/332) were commonly observed in females with the enzyme activity arranged 1.99 ± 1.33 IU/g·Hb and 3.26 ± 1.52 IU/g·Hb, respectively. The lower activity was significantly observed in hemizygous males than in heterozygous females ($p < 0.0001$), whereas a statistical difference was evaluated when a comparison of activity between homozygous females and heterozygous females was made ($p=0.04$) (Figure 1(b)). In terms of G6PD activity, the *Union* variant presented the lowest mean value (1.03 IU/g·Hb), followed by *Canton* (1.4 IU/g·Hb) and *Kaiping* variant (1.35 IU/g·Hb) (Figure 4(a)). Variant groups in which there were ≥2 representatives were shown in Figure 4. There was a significant difference between these variants and the enzyme activity ($p=0.0088$). In addition, the activity of the cooccurred variants was also presented, but no significant difference was recorded ($p=0.8139$) (Figure 4(b)). Among the coexistent variants, we found that only the *Viangchan/Silent* variants presented a correlation to the G6PD enzyme activity ($r=0.3186$, $p=0.0033$), while the other variants did not show the relationship.

Table 3

Variant patterns of G6PD and corresponding enzyme activities.

Variant patterns	Class	Male		Female			
Hemi	Enzyme activity (IU/g·Hb)	Homo	Enzyme activity (IU/g·Hb)	Hete	Enzyme activity (IU/g·Hb)	Valladolid	II
2	1.98	0	—	0	—	Nan Kang	II
1	1.7	0	—	0	—	Mediterranean	II
1	0.65	0	—	0	—	Coimbra Shunde	II
0	—	0	—	1	2.67	Viangchan	II
73	1.31	4	1.83	6	3.24	Union	II

41	0.66	1	0.12	9	2.8	Canton	II
55	1.26	0	—	5	2.98	Kaiping	II
72	1.32	1	1.28	3	2.13	Gaohe	III
22	1.34	0	—	2	4.15	Orissa	III
2	1.04	1	3.07	0	—	Quing Yan	III
10	2.05	0	—	2	5.19	Chinese-5	III
11	1.38	1	4.14	2	4.19	Taiwan 2	III

[figure(s) omitted; refer to PDF]

4. Discussion

G6PD deficiency is a common enzyme abnormality that affects approximately 5% of the world´s population and causes some diseases related to erythrocytes [24]. Some mutations on the G6PD gene are being investigated to be associated with this deficiency of the G6PD enzyme activity. Therefore, identifying G6PD variants plays an important role in screening and estimating the risk variants in communities.

The distribution of G6PD deficiency is variable across ethnic groups and geographical regions [13]. In our study, the 339 blood samples were selected from five ethnicities in Northern Vietnam including Kinh, Muong, Nung, Thai, and Tay. The results showed that while the Kinh ethnic group had the highest prevalence of G6PD deficiency (~60%), the Thai ethnic group carried the lowest G6PD distribution compared to the others (Figure 2(a)). The main distribution of G6PD deficiency in the Kinh ethnic group can be explained by the predominance of this ethnic group in Vietnam, accounting for approximately 86% of the population [25]. However, no statistically significant difference was observed between the G6PD incidence and ethnic groups ($p>0.05$). Similar results were reported in the Kinh and S'Tieng ethnic groups, according to Nguyen Thi Hue et al. (2009). Although the frequency of G6PD deficiency in Southern Vietnam was rather high, accounting for 11.3%, this proportion in the Kinh and S'Tieng populations was only 8.7% and 14%, respectively ($p=0.07$) [21]. Likewise, compared to Myanmar ethnicities, the Kachin people have a higher level of G6PD prevalence (29.6%) compared to other local groups such as Mon (12%), Burmese (10%), Karen (12.9%), and Burman [26–28]. Also, the variable of G6PD distribution was observed among the Lue ethnicities in Thailand. Although the rate of G6PD in the Lue ethnic group was 13.51%, the different local languages show the variation in Ta-Kadai (9.69%), Sino-Tibetan (4.51%), Austroasiatic (7.58%), and Hmong-Mien groups (1.77%) [29]. An extreme distribution of G6PD deficiency in the Great Mekong Subregion (GMS) countries can be understood because these countries were seriously affected by the malaria pandemic [30]. It could be a possible evolutionary factor to increase the prevalence of G6PD deficiency in the population.

Furthermore, our results indicated that males were more severely deficient in G6PD than females. This enzyme

activity in males (1.27 ± 1.06 IU/g·Hb) was significantly lower than in females (2.98 ± 1.57 IU/g·Hb) ($p<0.0001$) (Table 1; Figure 1(a)). Because the G6PD gene is located on the X chromosome, its expression can be different between both genders. Males have only one X chromosome and will be hemizygous with G6PD mutations [31]. Therefore, G6PD deficiency can express fully in this phenotype compared to that in females, which can be caused by X-inactivation [32, 33]. Females with G6PD heterozygous genotypes present a wide range decrease of G6PD activity, a range from 20–80% with the normal [34].

In this study, we identified 13 G6PD variants by Sanger sequencing. The majority of variants are chiefly discovered in China, India, and they have been established as Asia variants; the other is found in European origin countries and Mediterranean areas such as *Valladolid* and *Mediterranean* [12,13]. The finding supports the notion that the genetic drift event occurred in the Asian population in the prehistoric period. For example, the migration of Chinese to Vietnam has been recorded for a long time and gradually Vietnamized to be Hoa ethnics [35]. Ethnic migration is investigated to play a crucial role in regular genetic trait distribution and the characteristics of populations according to the gene flow process [36–38]. In Yuzhong Zhen's study, the heatmap for distribution of the G6PD-deficient allele indicates that Canton, Kaiping, and Gaohe are highly related to the Chinese population, the G6PD Viangchan and Mahidol were mostly related to the Southern Asian population. The ethnic migration suggested that the Chinese variants occurred before the formation of these Chinese ethnic populations [39].

Of 13 G6PD variants, we found that *Viangchan* variants had the highest frequency among our ethnic groups with 24.48% (Table 1). It has been considered the most common mutation in Asia with diverse distribution between regions and ethnicities. In Southern Vietnam, this variant is highly detected in the Kinh and K'Ho ethnic groups with 44%, and 75% is observed in the Raglai and Pako ethnic groups [22, 40]. In several countries of GMS, the *Viangchan* variant is found in Laotians (100%), Cambodians (97.9%), and Thais (67.7%) [16, 41, 42]. The sharing of G6PD *Viangchan* among Southeast Asian populations reveals insight into old ancestral sources in these countries. In addition, the *Canton* and *Kaiping* variants are the most prevalent in South West China with 20% and 79.16%, respectively, found in 17.7% and 24.2% of our samples [43]. Likewise, in Thailand, *Canton* and *Kaiping* are observed in 15.4% and 14.4% of G6PD deficiency cases, respectively [5]. The G6PD *Union,* which was presented at 15.04% in this study, is determined at 100% in the Khomu population and 9.5% in Thailand [20, 44]. On the other hand, G6PD *Gaohe* is also an important Chinese variant with an incidence rate ranging from 8.8% to 14.2% in different studies and was identified at about 7.08% in this study [45–47]. The Chinese variants including *Orissa* (0.88%)*, Quing Yan* (3.54%)*, NanKang* (0.29%)*, Taiwan-2* (0.29%)*, Chinese-5* (0.29%)*,* and *Coimbra Shunde* (0.29%), and European variants such as *Valladolid* (0.59%) and *Mediterranean* (0.29%) were rarely detected in Northern Vietnam but were observed in several studies with various frequencies [5, 18, 29, 48–51]. Moreover, *Silent* variants are the most common polymorphism of G6PD gene and have a high rate of distribution among populations [18, 21, 29].

To date, *in silico* analysis has been applied to estimate the pathogenic mutations for disease. In the current study, the Polyphen-2 tool reported *Mediterranean*, *Chinese-5*, and *Taiwan-2* variants as benign, whereas the other variants were damaged, almost similar to the G6PD classification of WHO (Tables 2, 3). These results suggest that all G6PD variants can be caused by G6PD deficiency. The application of bioinformatics tools in G6PD mutations has been investigated in different populations [52–54]. In Chinese ethnicity, the lowest enzyme activity is G6PD *Canton* variant, which was recorded in the *Union* variant of our data [18]. In addition, the *Mediterranean* variant, which is considered more severe by the WHO classification, was found to be benign through bioinformatic analysis in this study. The different results can be understood by the variable of gene expression within and between populations [55]. Although the *Silent* variant is a silent mutation in the intronic region, it has been investigated relatively to G6PD deficiency [56]. Some hypotheses are postulated to interpret the expression of enzyme activity of this mutation. By predicting the secondary structure of G6PD mRNA, the mutant *Silent* presents the stable structure at the start codon boundary, therefore causing a negative effect on mRNA translation [57]. Or this single mutation may be located in the enhance region, where nucleotide alteration can change the function and lead to reduced gene expression [58]. Thus, further studies should be performed to clarify the mechanism of the *Silent* variant. Among coexistent variants,

the linkage disequilibrium between G6PD *Viangchan* and *Silent* was the most common, occurring in Thai, Vietnamese, and Chinese populations [42, 58, 59]. However, the correlation of these covariants to the G6PD enzyme activity is not fully understood.

5. Conclusions

In this study, we successfully identified 13 G6PD variants related to G6PD deficiency in Northern Vietnam by Sanger sequencing. G6PD *Viangchan, Canton, Kaiping,* and *Union* variants were the most prevalent across Vietnamese ethnic groups, accounting for 79.64% of samples. In addition, the six cooccurred variants were also observed at different frequencies. The correlation between these single variants and G6PD deficiency was investigated by a bioinformatic tool, further studies should be performed on coexistent mutations. The result will contribute to the diagnosis and screening of G6PD deficiency in Vietnam, reduce consequences for the patient's family and society, as well as improve the quality of health care in the community.

Authors' Contributions

Thi Thao Ngo and Thinh Huy Tran contributed equally to this work.

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DETAIL

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Hematological Parameters in Individuals with Beta Thalassemia Trait in South Sumatra, Indonesia

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ABSTRAK (ENGLISH)

Background. β-Thalassemia has a very wide clinical variation, depending on the severity of the patient's condition. Individuals with β-thalassemia traits are usually asymptomatic; however, laboratory examination will show mild anemia with microcytic hypochromic erythrocytes morphology with wide variation depending on the genotype. This study was conducted to determine the reference value of hematological parameters and hemoglobin (Hb) analysis based on the phenotype of β-thalassemia (β^0 and β^+) and determine the differences of hematological characteristics between the two phenotypes. *Methods*. This cross-sectional study was conducted by evaluating the hematological parameters and Hb analysis of the β-thalassemia trait in the family of thalassemia patient population. The subjects were divided into β^0 and β^+. The subject with normal Hb analysis with or without iron deficiency was excluded. *Results*. A total of 203 subjects with thalassemia traits were included from the families of thalassemia patients, consisting of 101 subjects with β^0-thalassemia, 82 subjects with β^+-thalassemia, and the mutation had not been found in 20 subjects. There was a relationship in the mean/median of hematological parameters, HbA_2 and HbF, between β^0-thalassemia and β^+-thalassemia ($P<0.05$). ROC for each hematological parameter, HbA_2 and HbF, showed that the highest diagnostic value based on the area under the curve was mean corpuscular hemoglobin (MCH) (0.900) and mean corpuscular volume (MCV) (0.898). The cutoff point of MCH for β^0-thalassemia trait was ≤20.5 pg (sensitivity 85%, specificity 90%) and MCV was ≤66.8 fL (sensitivity 87%, specificity 87%). *Conclusion*. MCH values can be used as a screening tool for predicting β^0-thalassemia in the relatives of thalassemia patients in the South Sumatra population.

TEKS LENGKAP

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1. Introduction

Thalassemia is an autosomal recessive genetic disorder characterized by hemolytic anemia. β-Thalassemia is caused by abnormalities of the single β-globin gene that interfere with the synthesis of the globin chains of hemoglobin; this interference can cause total (β^0) or partial (β^+) disruption of globin chain synthesis [1, 2]. Currently, thalassemia is the most widespread monogenic disease in the world. Based on the WHO, in 2008, at least 5.2% of the world's population were thalassemia carriers, 1.1% of which were couples that had a risk of having children with hemoglobin disorders [3]. The prevalence of trait carriers was found to be very high in the populations of Africa, Southeast Asia, the Eastern Mediterranean, and the Western Pacific [4]. Southeast Asia is the region with the most complex thalassemia genotype compared to other countries. South Sumatra is one of the areas with the highest carrier rates for hemoglobinopathies in Indonesia, with the prevalence being 15%, consisting of 9% carriers of β-thalassemia trait and 6% HbE [5].

β-Thalassemia has a very wide clinical variation, depending on the severity of the patient's condition and age at the time of diagnosis. Thalassemia traits is asymptomatic; however, laboratory examination will show variation of Hb levels; it could be normal to up to 2 g/dL, with microcytic hypochromic erythrocytes [6]. Hemoglobin analysis will demonstrate an increase in HbF and HbA2 levels. The Indonesian thalassemia management guidelines recommend the routine use of erythrocyte index as a screening tool in patients with thalassemia. Based on this guideline, patients with MCV <80 fL and MCH <27 pg should be evaluated further. In Indonesian Guideline for Management of Thalassemia (2018), possibility of thalassemia traits is identified by HbA_2 examination: an HbA_2 level between 3.6 and 4.2% suggests mild β^+-thalassemia and levels between 4 and 9% suggest heterozygote β^0-thalassemia and severe β^+-thalassemia [7]. This study was conducted to determine the appropriate reference value of hematological parameters and Hb analysis based on the phenotype of β-thalassemia (β^0 and β^+) and determine the differences of hematological characteristics between the two phenotypes.

2. Methods

The cross-sectional study was conducted at the Thalassemia Center in Mohammad Hosein General Hospital (RSMH), Palembang, from October 2020 to December 2020. RSMH is the tertiary hospital which cover the South Sumatera region. The ethical clearance of this study was approved by RSMH (Letter No.: 111/kepkrsmh/2020) and RSCM-FKUI (Letter No.: KET-1369/UN2.F1/ETIK/PPM.00.02/2020) Ethical Committee. Research subjects are parents and siblings of thalassemia patients who routinely receive blood transfusions. The method uses consecutive sampling; subjects were recruited until the minimum sample size was reached, until it meets the number of samples, or until the end of the study.

Written consent was obtained from all subjects who were willing to participate. Subjects were enrolled consecutively from relatives of patients who received regular blood transfusion in RSMH. For children under 18 years of age, consent was obtained from their parents. The screening was carried out in the form of interviews, physical examination, and blood collection for hematological examination, Hb analysis, and DNA analysis. Interviews were conducted to determine the identity, ethnic origin, and history of transfusion. The ethnic groups were grouped based on the origin of the South Sumatran and non-South Sumatran tribes. Physical examination included an examination for clinical symptoms such as pallor and splenomegaly. 15 mL of blood was collected intravenously for hematological examination, Hb analysis, iron status, and DNA analysis. We excluded the subjects with normal Hb analysis with or without iron deficiency. Hb analysis was normal if HbA_2 is <3.5%, HbF <1%, and HbA >97% [7]. Iron deficiency was defined if ferritin serum was <12 ng/mL for under 5 years old subjects and <15 ng/mL in subjects ≥5 years old [8]. DNA analysis was not performed on subjects who had normal Hb analysis or evidence of iron deficiency. *β*-Thalassemia mutation type was determined by DNA analysis using the PCR-RFLP technique followed by DNA sequencing. Examination of mutations in exons 1 and 2 and intron 1 that often appears in Indonesia was carried out on all subjects. In subjects whose mutations were unidentified, the examination was continued on exon 3. The types of globin gene mutation were grouped according to the *β*-globin synthesis phenotype. β^0-Thalassemia is the phenotype of a mutation that causes the *β*-globin chains do not produce, such as mutations in IVS1-nt5 (G C), IVS1-nt1 (G T), CD15 (TGG TAG), CD17 (AAG TAG), CD30 (+C), CD 35 (−C), CD41-42 (−TCTT), CD8/9 (+G), IVS1-nt2 (T C), and CD 26 (GAG TAG), whereas in β^+-thalassemia, *β*-globin chains were formed, but has declined in function, which included the mutations in CD 19 (AAC AGC) and CD-26 (GAG AAG)/HbE. [9].

2.1. Statistical Analysis

Descriptive data in the form of mean, median, and range were used to describe the distribution of numerical data (Hb, erythrocyte index, Hb analysis). Data analysis was conducted to determine the relationship between thalassemia mutation phenotype with Hb levels, MCV, MCH, MCHC, RDW, and Hb analysis using an independent *t*-test. The assessment of the cutoff point of each variable that had a relationship was using ROC curve. The diagnostic value (sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive, and likelihood ratio negative) was calculated. The analysis was carried out using the SPSS version 20 for Windows.

3. Results

There were 224 subjects in the current study, consisting of 203 subjects who were carriers based on Hb analysis and DNA analysis and 21 subjects who had normal Hb analysis, in which 3 had iron deficiency anemia.

The carriers consisted of 154 subjects who are parents, 24 subjects are siblings, 4 subjects are uncles, and 1 subject is a cousin of thalassemia patients who has routinely received transfusions at RSMH. The characteristics of the subjects are given in Table 1. Most of the subjects carrying the trait were females (64.5%); the median age was 37.3 (2.3–64.5) years and came from the South Sumatran ethnic group (70.4%). Most of the subjects lived outside of Palembang city (56.7%). Based on DNA analysis, 20 subjects had no mutation identified yet, but the hematologic features, Hb analysis, and iron status suggested to thalassemia condition, consisting of 18 subjects are parents and 2 subjects are siblings.

Table 1

Characteristics of the subject of the trait carrier (*n*=203).

Characteristics	*N*	%
–		
Age group (years)		
2–10	15	7.4
>10	188	92.6
–		
Gender		
Male	72	35.5
Female	131	64.5
–		
South Sumatra ethnic group		
Yes	143	70.4
Not	60	29.6
–		
Mutation type		
β^0-Thalassemia heterozygotes	101	49.7
β^+-Thalassemia heterozygotes	82	40.3
The mutation was not found[†]	20	10

[†]Mutation was not found in exon 1, exon 2, exon 3, and several introns that are often populated by Indonesia.

The type of mutation grouped by the *β*-globin chain synthesis is given in Table 2. We identified two types of heterozygotes, β^+-thalassemia mutations and 10 types of β^0-thalassemia mutations. The most common mutations found were mutations in IVS1-nt5 heterozygotes in 59 (32.2%) subjects, followed by HbMalay heterozygotes in 47 (25.7%) subjects, HbE heterozygotes in 35 (19.1%) subjects. IVS1-nt1 heterozygotes in 16 (8.7%) subjects, CD 41–42 (−TCTT) heterozygotes in 14 (7.7%) subjects, CD 8/9(+G) heterozygotes in 4 (2.2%) subjects, CD 35(−C) heterozygotes in 3 (1,6%) subjects, and CD15, CD26 (G T0), and CD 30 heterozygotes mutation each in one subject (2.5%).

Table 2

Types of *β*-thalassemia mutations found in the present study (*n*=183).

Mutation type	*N* = 183	%
–		
β^0-Thalassemia heterozygote		
IVS1-nt5 (G C)	59	32.2
IVS1-nt1	16	8.7
CD 41–42 (−TCTT)	14	7.7
CD 8/9 (+G)	4	2.2
CD 35 (−C)	3	1.6
CD 15	1	0.5
CD 26 (G > T)	1	0.5
CD 30	1	0.5
CD 71/72 (+A)	1	0.5
IVS1-nt2	1	0.5
β^+-Thalassemia heterozygote		
HbMalay	47	25.7
HbE	35	19.1

Table 3 provides hematological parameters and Hb analysis by type of mutation. There were statistically significant differences in the mean/median Hb, MCV, MCH, MCHC, RDW, HbA_2, and HbF, where Hb, MCV, MCH, and MCHC levels were lower in β^0-thalassemia compared to β^+-thalassemia. Meanwhile, the RDW level was higher. Besides, based on Hb analysis, HbA_2 and HbF levels were higher in β^0-thalassemia compared to β^+-thalassemia with a P value <0.05.

Table 3

Hematological variables among β^0 and β^+-thalassemia carrier.

Variable	β^0-Thalassemia (*N* = 101)	β^+-Thalassemia (*N* = 82)	P value
–			
Hematological parameter			

Hb (g/dL)*	11.4±1.2	12.4±1.4	<0.001‡
MCV (fL)**	63.6±4.8	72.05±5.3	<0.001‡
MCH (pg)**	19.5±1.8	23.1±2.3	<0.001‡
MCHC (g/dL)	30.7±0.9	31.9±1.4	<0.001‡
RDW (%)**	17.4±1.7	15.6±1.7	<0.001‡
–			
Hemoglobin analysis			
HbA_2 (%)**	5.02±0.8	4.3±0.6	<0.001‡‡
HbF (%)**	0,91±1,8	0.8±2.8	0,040‡‡
HbA (%)**	93.7±3.05	85.9±11.6	0.078‡‡

*Normal distribution,**abnormal distribution, ‡Independent *t*-test,‡‡Mann–Whitney test.

Table 4 provides the hematological parameters and Hb analysis of each genotype (CD 35 (−C), CD 41–42 (−TCTT), CD8/9 (+G), IVS1-nt1, IVS1-nt5, HbE, and HbMalay). HbE and HbMalay was frequent mutation in South East Asia region; this study showed that Hb, MCV, and MCH level of HbE trait was greater than HbMalay trait, while the RDW was lower.

Table 4

Distribution of hematological parameters and Hb analysis for each genotype.

Genotype	β^0 heterozygotes				β^+ heterozygotes		
CD 35 (−C)	CD 41–42 (−TCTT)	CD 8/9 (+G)	IVS1-nt1	IVS1-nt5	HbE	HbMalay	*n*=3
n=14	*n*=4	*n*=16	*n*=59	*n*=35	*n*=47	·	
Hematological parameter							
Hb (g/dL)**	12.1 (10.8–12.3)	10.9 (8.8–13.5)	12.1 (11.1–13.0)	11.0 (9.4–13.3)	11.4 (9.3–14.6)	12.7 (9.5–15.1)	12.3 (8.3–15.5)
MCV (fL)**	65.9 (63.3–68.3)	60.2 (55.6–63.4)	61.3 (61.1–61.5)	62.5 (54.4–85.3)	63.9 (51.9–79.5)	75.2 (61.9–83.3)	71.2 (53,4–81,3)
MCH (pg)**	20.0 (20.0–21.0)	18.5 (17.0–20.0)	18.0[a]	19.0 (17.0–28.0)	20.0 (15.0–26.0)	24.0 (18.0–30.0)	22.0 (16.0–25.0)

RDW (%)**	15.6 (14.5–17.7)	18.0 (15.4–20.8)	18.2 (17.6–19.1)	17.5 (12.1–20.1)	17.2 (12.6–20.2)	14.6 (12.3–18.3)	15.6 (13.5–20.6)
–							
Hemoglobin analysis							
HbA2 (%)**	5.4 (5.1–5.4)	5.5 (4.9–6.6)	4.8 (4.7–5.3)	5.2 (2.7–6.1)	5.0 (1.9–6.4)	3.7 (2.9–5.7)	4.5 (3.7–6.0)
HbF (%)**	0 (0–1.4)	0.4 (0–2.9)	0.7 (0–0.4)	0.7 (0–4.1)	0 (0–12.7)	0 (0–24.5)	0.2 (0–3.9)
HbA (%)**	94.6 (93.2–94.9)	93.9 (90.5–95.1)	95.2 (94.3–95.3)	93.6 (90.7–96.8)	94.6 (70.9–98.1)	71.1 (68.0–94.8)	95.1 (91.4–96.3)
HbE (%) (*n*= 35)**					1 subject: 25.4	25.2 (23.0–27.0)	

**Abnormal distribution (median). [a]MCH value in CD 8/9(+G) mutation has the constant value (4 subjects) = 18 pg.

The diagnostic values (sensitivity, specificity, positive and negative predictive value, likelihood ratio positive and negative, and characteristic ROC) in connection with the cutoff in this population for differential diagnosis of β^0-thalassemia compared to β^+-thalassemia are given in Table 5.

Table 5

Evaluation of different hematological parameters and Hb analysis in the differentiation of β^0-thalassemia compared to β+-thalassemia.

	Sensitivity	Specificity	PPV (%)	NPV (%)	LR +	LR −	Cutoff for β^0 in our population	AUC (95% CI)
–								
Hematology parameter								
Hb	78	56	69	68	1.78	0.39	≤12.3	0.702 (0.625–0.778)
MCV	87	87	89	85	2.71	0.29	≤66.8	0.898 (0.847–0.948)
MCH	85	90	91	83	8.73	0.16	≤20.5	0.900 (0.849–0.952)
MCHC	86	60	73	78	2.14	0.23	≤31.5	0.784 (0.716–0.851)
RDW	79	71	77	73	0.29	2.71	≥16.15	0.211 (0.142–0.280)

–								
Hemoglobin analysis								
HbA_2	88	74.4	81	84	3.44	0.16	≥4.65	0.844 (0.781–0.906)
HbF	58	61	65	54	1.50	0.68	≥0.35	0.583 (0.500–0.667)

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; AUC, area under the curve.

Figure 1 shows ROC for hematological parameter calculation, and Figure 2 shows ROC for Hb analysis calculation. From Table 5, Figures 1 and 2, the highest diagnostic value was related to MCH to differentiate β^0-thalassemia compared to β^+-thalassemia. There was no significant difference in the AUC of HbF levels between these types of mutation.

[figure(s) omitted; refer to PDF]

4. Discussion

Southeast Asia region has the most complex genotypes of thalassemia in the world as the result of various combinations of globin chain gene mutations from interethnic marriage [10]. South Sumatra has a high carrier prevalence of β-thalassemia trait as much as 15% [11], so that screening is necessary to prevent the birth of children with thalassemia major. In the current study, analysis of 183 subjects was conducted to compare the hematological parameters between β^0-thalassemia compared to β^+-thalassemia carriers in the families of thalassemia patients to determine the predictive value that can be used as a screening tool. The current study found 12 types of mutations in 183 subjects, with the most common mutations being IVS1-nt5 (32.2%), followed by HbMalay (25.7%) and HbE (19.1%). A previous study in 2003 that examined trait-carrying mutations in the Malay ethnicity of South Sumatra in the general population found that the most common mutations were HbE (36.3%), followed by HbMalay (34.09%) and IVS1-nt5 (9.09%) [5].

Erythrocyte index (MCV and MCH) is a parameter used in screening for thalassemia, based on the International Thalassemia Federation (TIF) guidelines. Levels of MCV <78 fL and MCH <27 pg, with peripheral blood features of microcytic, hypochromic, and anisopoikilocytosis can be suspected as carriers [1]. Based on Indonesia Guidelines for Management of Thalassemia, the suspected carriers in general population, if the MCV value was <80 fL and the MCH value was <27 pg [7].

In the current study, the mean of Hb, MCV, MCH, and MCHC in β^0-thalassemia was lower than β^+, besides the RDW, $HbA_{2,}$ and HbF levels were higher. These data could explain the differences between the two phenotypes to define cutoff values for each variable. Indonesia, especially South Sumatra, have various ethnic groups. The cutoff points of hematological parameters and Hb analysis can be useful to differentiate the type of thalassemia mutation in the carrier population in South Sumatra for screening purposes in the families of thalassemia patients. Evaluation of hematological parameters and Hb analysis in this study was performed and compared according to the ROC curve. The result shows that MCH has the largest AUC (0.900).

Hematological characteristics of β-thalassemia heterozygotes have wide variation based on the type of mutation [12, 13]. Baliyan et al.' [14] study in India showed that MCV <74 fL combined with MCH <28 pg can be used as a cutoff for the screening test of thalassemia in antenatal anemic woman in South Asian region, if the HPLC in the facility does not exist (sensitivity 95%, specificity 16%). Another study in Iran showed that MCH <27 pg was more sensitive compared with MCV <80 fL for screening of β-thalassemia traits in the general population [15]. The study in Israel [16] showed that there was a relationship between MCH and type of mutation with cutoff point 20.94; however, MCH was less sensitive to differentiate between β^0 and β^+ populations. This present study found that MCH value ≤ 20.5 pg was predicted as β^0-thalassemia (sensitivity 85%, specificity 90%, PPV 91%, NPV 83%, and likelihood ratio positive 8.73).

A study in Israel showed that MCV lower than 66.96 fL could predict the possibility of β^0 mutation (sensitivity 77% and specificity 91%) [16]. Almost similar to this present study, we found the cutoff point of MCV was ≤66.8 fL (sensitivity 87%, specificity 87%) for β^0 and >66.8 for β^+.

The RDW examination is usually done to differentiate between iron deficiency anemia and thalassemia independent of transfusion. The cutoff >14% suggests thalassemia trait carriers [17]. In the present study, we found significant differences in the levels of RDW between β^0-thalassemia and β^+-thalassemia with $P<0.05$. The median RDW is known to be lower in β^0-thalassemia compared to β^+-thalassemia. In the study done in Medan, North Sumatra (2019) [18], the RDW level in carriers of β-thalassemia trait was between 15.7% and 16.5%, while this present study has a wider range of RDW which was 12–20.8%.

Based on Hb analysis, we found that there are significant differences between the levels of HbA_2 and HbF in β^0-thalassemia and β^+-thalassemia, where the levels of HbA_2 in β^0-thalassemia were between 1.7 and 6.6% with a median of 5.1%. The lower levels found in the current study compared to the threshold used by the guidelines used for the screening of thalassemia in which levels of HbA_2 in thalassemia suggestive of β^0-heterozygotes were 4–9% and in β^+-thalassemia between 2.9 and 6% with a median of 4.3%. HbA_2 levels can also be affected by iron status, whereas in deficiency anemia, HbA_2 levels will decrease [7]. The HbA_2 level used in screening to detect thalassemia is >3.5%. However, in this study, 6.6% of subjects had HbA_2 2 of β^0-thalassemia in this study using the ROC curve, finding that HbA_2 level ≥ to 4.65% was predicted to be β^0-thalassemia, with sensitivity 88% and 74% of specificity. The HbA_2 value in this subject could be affected by iron status; there were 5 subjects who had iron deficiency, and those are 2/101 subjects with β^0-thalassemia and 3/82 subjects with β^+-thalassemia.

From the current study, we concluded that MCH can be used as a screening tool to differentiate the type of β-thalassemia mutation (β^0 or β^+) in populations of carriers consisting of relatives of patients with thalassemia in South Sumatra.

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DETAIL

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Anemia Burden among Hospital Attendees in Makkah, Saudi Arabia

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ABSTRAK (ENGLISH)

Background. Anemia is a major health problem in Saudi Arabia and has multiple etiologies. Many studies have been conducted in Saudi Arabia in specific population groups like school children, adolescents, university students, and females in the reproductive age group, and most have reported high prevalence of anemia. This study was conducted in a specialist hospital in Makkah city and includes all outpatients aged 15 years and above. *Objective*. To study the burden of anemia among hospital attendees, its stratification based on gender and age, and its severity along with the morphological types of anemia. *Methods*. This is a study conducted at a specialist hospital in Makkah city and one-month data were collected retrospectively from the laboratory database and include demographic and routine hematological results of complete blood count (CBC). *Results*. A total of 21,524 patients were included, out of which 9444 (43.9%) were males and 12020 (56.1%) were females. The overall prevalence of anemia was 38.7% (8339). Prevalence was very high in females, accounting for 68.2% (5689), whereas it was 31.8% (2650) in males. There were 39.6% (3301), 43.9% (3657), and 16.6% (1381) cases of mild, moderate, and severe anemia, respectively. In females, anemia was more prevalent in the age group of 15 to 49, which is considered as the reproductive age group. Microcytic anemia was the most prevalent type observed in this age group, accounting for 40.7% of all anemia cases. Normocytic anemia was more prevalent in the males, accounting for 52%. *Conclusion*. Our study showed high prevalence of anemia among the patients attending outpatient departments in a specialist hospital. Females have high prevalence of anemia when compared to male population. Microcytic anemia was the most common anemia type among females and was seen in the 15–49 age group. There is an increase in prevalence of anemia with age for males, whereas, in females, increased prevalence is observed in the reproductive age groups and the anemia prevalence maintained a steady decrease towards the 5th to the 9th decades. Normocytic anemia was more prevalent in the 5th to the 9th decades, indicating that there are more etiologies other than iron deficiency in the causation of anemia. Macrocytic anemia was the least reported anemia type. Anemia of mild and moderate severity was predominant in both genders, although severe anemia showed higher prevalence in females as compared to males. *Conclusion*. Anemia is highly prevalent in adolescents, adults, and the elderly in Makkah region. The most common cause is thought to be iron deficiency, although other causes are not uncommon. The authorities need to address the problem of prevention and reduction in anemia prevalence by taking effective measures and interventions.

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1. Introduction

Anemia is a global health issue affecting a quarter of the global population [1]. It affects almost every country and occurs in all age groups but is more prevalent during pregnancy and childhood [2]. In many developing countries, anemia has reached the level of an epidemic [3]. It is reported that half of the cases of anemia are due to iron deficiency, which is the most common micronutrient deficiency [4, 5]. Along with nutritional deficiencies, malaria, parasitic infections, blood loss, hemoglobinopathies, and bone marrow suppression or replacement are common etiologies [6]. Anemia is defined by WHO as a condition in which hemoglobin concentration is below 120 g/L in nonpregnant females and below 130 g/L in males [2]. Iron deficiency causes chronic fatigue and tiredness and can affect cognitive functions, as well as motor and mental development along with visual and auditory functions of

people [7]. Anemia is found in varying degrees across the world, depending on the age group and geographic location. Anemia affects one out of every four people, with pregnant women and children under the age of five being the most vulnerable. With two-thirds of preschool-aged children and half of all women impacted, the WHO areas of Africa and Southeast Asia are the most at risk [2]. In terms of numbers, the majority of the burden is concentrated in South-East Asia, where roughly 40% of anemic preschool-age children and nonpregnant women, as well as approximately 30% of pregnant women, reside [8].

WHO has reported global prevalence of 30.2% among nonpregnant women (15–49.99 years) and about 33% in Asia and 44.4% in Africa. Among men (aged 15–59.99 years) and the elderly (≥60 years), the global anemia prevalence is 12.7% and 23.9%, respectively [2].

Anemia is a common problem in low- and middle-income countries, particularly among adolescent females, women of reproductive age, pregnant women, and children. Anemia is expected to be reduced in women of reproductive age (15–49 years) by 50 percent by 2025, according to the second of the world's six global nutrition objectives. Given the fact that anemia affects half a billion women of reproductive age around the world, eliminating anemia is essential for the health as well as their economic production. According to the Global Health Observatory, anemia prevalence among women of reproductive age ranged from 9.1 percent in Australia to 69.6 percent in Yemen in 2016 [8].

According to reports, anemia is a significant health burden in the Gulf countries, with a high frequency of anemia in females between the ages of 17 and 24 years, as well as males, being reported [4]. Preschool children, pregnant women, and nonpregnant women all have high prevalence of anemia in Saudi Arabia, which, according to the World Health Organization's report on the worldwide prevalence of anemia, is considered a moderate health problem in the country, with prevalence ranging between 20.0 and 39.9 percent [2].

According to the findings of a study conducted on Saudi women aged 15–49 years, anemia was found in 40% of the participants [9]. Another investigation by Al Quaiz found a significant frequency of anemia among females from Riyadh, with an estimated 37 percent of females suffering from the condition [7]. Many studies have been undertaken in various population groups such as school children, teenagers, university students, and females in the reproductive age group in Saudi Arabia, and the findings have revealed a high incidence of anemia in these categories in the country [5, 10–13]. In this study, we aimed to determine the prevalence of anemia, its stratification based on gender, its severity, and the morphological type of anemia in all of the study patients.

2. Materials and Methods

This study was done using the patient's data collected retrospectively for one month from a specialist hospital in Makkah city. The data were collected from the laboratory database and include demographic and routine hematological results of complete blood count (CBC) performed on a fully automated hematology analyzer. Hematological data from all patients aged 15 years and above and attending the routine outpatient departments over a period of one month from January 1, 2019, to January 31, 2019, were included for analysis.

The hemoglobin cut-off (g/L) for the diagnosis of anemia and its categorization based on severity into mild, moderate, and severe anemia was done as per WHO recommendation as shown in Table 1 [14].

Table 1

Hemoglobin levels for stratification into mild, moderate, and severe anemia [14].

	Nonanemia	Anemia

Mild	Moderate	Severe	Nonpregnant women (15 years of age and above)	120 or higher
110–119	80–109	<80	Men (15 years of age and above)	130 or higher

Statistical Analysis was done using IBM SPSS Statistic (Statistical Package for the Social Sciences, version 20, Armonk, New York, USA). P value <0.05 was considered statistically significant. Continuous variables were expressed as mean ± standard deviation and categorical data were presented as median and interquartile range (IQR). Odds ratios (ORs) and 95% confidence intervals were obtained by logistic regression to determine the impact of age on anemia.

3. Results

The specialist hospital lab receives between 400 and 500 blood samples for routine hematological tests every day from patients attending the outpatient clinics. A total of 21,524 patients were included, out of which 9444 (43.87%) were males and 12020 (56.2%) were females (Figure 1). The mean age for male patients was 48.83 ± 18.7, with a range of 15 to 89 years, and for females it was 46.88 ± 17.8, with a range of 15 to 88 years. We included 21,524 hemoglobin estimations and none of the patients had repeated hemoglobin value. The overall prevalence of anemia was 38.7% (8339). Among all the anemia cases, prevalence was very high in females, accounting for 68.2% (5689), whereas it was 31.8% (2650) in males. Table 2 shows the hematological variables for male and female patients. Overall, there were 39.6% (3301), 43.9% (3657), and 16.6% (1381) cases of mild, moderate, and severe anemia, respectively. The mean hemoglobin concentration was 125.29 ± 25.7. The mean hemoglobin in males was 100.12 ± 19.2 g/l and in females it was 98.8 ± 18.2 g/l. Tables 3 and 4 along with Figures 2 and 3 present the age-wise distribution of hemoglobin and stratification into mild, moderate, and severe anemia based on WHO recommendation for males and females, respectively [14].

[figure(s) omitted; refer to PDF]

Table 2

Hematological variables and demographic data.

Variable	Mean	SD	Minimum value	Maximum value	Median
Age (years)					
Male	48.84	18.17	15	89	46
Female	46.88	17.8	15	88	47
–					
Hb level (g/dl)					

Male	100.12	19.2	3.12	21.5	14.3
Female	98.8	18.2	2.56	23.3	12.1
–					
Mean cell volume (μm^3)					
Male	83.86	6.56	47.8	138.9	84.5
Female	81.77	7.80	46.6	120.6	82.88
–					
MCH (pg)					
Male	28.08	2.71	12.3	54.6	28.58
Female	26.65	3.27	13.15	59.60	27.3
–					
MCHC (g/dl)					
Male	32.4	38.12	8.26	64.3	33.35
Female	31.3	39.57	7.57	70.5	32.45
–					
RDW (%)					
Male	14.13	2.03	10.9	35.5	13.6
Female	14.91	2.31	11	32.7	14.28
–					
RBC (m/µl)					
Male	5.05	0.75	1.35	10	5.12
Female	4.54	0.56	1.75	7.43	4.56

Table 3

Severity of anemia across age groups in males.

			Age groups								Total
≤19	20–29	30–39	40–49	50–59	60–69	70–79	>80	HGB categories	Severe anemia	Count	29
64	65	45	55	73	48	25	404	% of total	1.1%	2.4%	2.5%
1.7%	2.1%	2.8%	1.8%	0.9%	15.2%	Moderate anemia	Count	59	126	130	119
159	205	141	102	1041	% of total	2.2%	4.8%	4.9%	4.5%	6.0%	7.7%
5.3%	3.8%	39.3%	Mild anemia	Count	68	100	129	118	202	273	210
105	1205	% of total	2.6%	3.8%	4.9%	4.5%	7.6%	10.3%	7.9%	4.0%	45.5%
–											
Total		Count	156	290	324	282	416	551	399	232	2650

Table 4

Severity of anemia across age groups in females.

			Age groups								Total
≤19	20–29	30–39	40–49	50–59	60–69	70–79	>80	HGB categories	Severe anemia	Count	48
146	176	201	149	116	92	49	977	% of total	0.8%	2.6%	3.1%
3.5%	2.6%	2.0%	1.6%	0.9%	17.2%	Moderate anemia	Count	117	346	527	536
370	375	225	120	2616	% of total	2.1%	6.1%	9.3%	9.4%	6.5%	6.6%

4.0%	2.1%	46.0%	Mild anemia	Count	91	353	371	388	356	303	157
77	2096	% of total	1.6%	6.2%	6.5%	6.8%	6.3%	5.3%	2.8%	1.4%	36.8%
–											
Total		Count	256	845	1074	1125	875	794	474	246	5689

[figure(s) omitted; refer to PDF]

All the anemia cases were categorized into microcytic, normocytic, and macrocytic anemia based on the reference cut-off for mean corpuscular volume (MCV). Microcytic anemia was the most prevalent type among females, whereas normocytic anemia was more prevalent in the males, accounting for 52% of the anemia cases in males (Tables 5 and 6; Figures 4 and 5). The prevalence of macrocytic anemia was very low in both genders. Among the male patients, high prevalence of mild and moderate anemia is observed in all age groups, although the 6th, 7th, and 8th decades showed increased prevalence, whereas severe anemia was distributed uniformly over all the age groups. In females, anemia was more prevalent in the age group of 15 to 49 which is considered as the reproductive age group. Microcytic anemia was the most prevalent type observed in this age group, accounting for 40.7% of all anemia cases (Table 6). After performing regression analysis for determining the impact of age on anemia, the ORs (95% CI) for severe, moderate, and mild anemia were 1.007 (1.004–1.01, P<0.001), 1.011 (1.009–1.013, P<0.001), and 1.013 (1.011–1.016, P<0.001), respectively. The OR for microcytic anemia was 0.984 (0.982–0.985, P<0.001) and for macrocytic anemia it was 1.014 (1.002–1.025, P=0.022).

Table 5

Prevalence of morphological types of anemias across age groups in males.

			Age groups								Total
≤19	20–29	30–39	40–49	50–59	60–69	70–79	>80	MCV groups	Microcytic	Count	109
167	159	142	182	260	146	84	1249	% of total	4.1%	6.3%	6.0%
5.4%	6.9%	9.8%	5.5%	3.2%	47.1%	Normocytic	Count	47	123	158	135
234	286	249	145	1377	% of total	1.8%	4.6%	6.0%	5.1%	8.8%	10.8%
9.4%	5.5%	52.0%	Macrocytic	Count	0	0	7	5	0	5	4
3	24	% of total	0.0%	0.0%	0.3%	0.2%	0.0%	0.2%	0.2%	0.1%	0.9%

–										
Total	Count	156	290	324	282	416	551	399	232	2650

Table 6

Prevalence of morphological types of anemias across age groups in females.

			Age groups								Total
≤19	20–29	30–39	40–49	50–59	60–69	70–79	>80	MCV groups	Microcytic	Count	202
629	824	857	540	419	215	98	3784	% of total	3.6%	11.1%	14.5%
15.1%	9.5%	7.4%	3.8%	1.7%	66.5%	Normocytic	Count	53	209	245	261
325	369	254	144	1860	% of total	0.9%	3.7%	4.3%	4.6%	5.7%	6.5%
4.5%	2.5%	32.7%	Macrocytic	Count	1	7	5	7	10	6	5
4	45	% of total	0.0%	0.1%	0.1%	0.1%	0.2%	0.1%	0.1%	0.1%	0.8%
–											
Total		Count	256	845	1074	1125	875	794	474	246	5689

[figure(s) omitted; refer to PDF]

4. Discussion

This study was done using the patient's data collected retrospectively for one month from a specialist hospital in Makkah city. In this study, we attempted to analyze the anemia prevalence among the outpatient attendees in various speciality departments. Anemia is a complex disease with nutritional and nonnutritional variables and mechanisms at play. Saudi Arabia, along with the Gulf Arab countries and others, is located in the eastern Mediterranean. In the eastern Mediterranean region, anemia prevalence ranges from 22.6 percent to 63 percent among pregnant women and is 69.6 percent among women of reproductive age [15]. Anemia was found to be prevalent in a high proportion of the patients in this study, according to the findings. The significant prevalence of microcytic anemia in females in the reproductive age range was identified, indicating that iron deficiency is the most likely cause of the condition. It is possible that malnutrition, increased blood loss due to pregnancy or menstruation, and a lack of iron absorption are the primary causes of this condition [6]. Because the serum ferritin levels were not available, we did not corroborate the findings. There have been numerous studies in Saudi Arabia which have revealed a significant frequency of iron deficiency anemia (IDA) in women of reproductive age in the country. IDA is prevalent in 41.6 percent of women between the ages of 18 and 40, according to Alswalem AM [16], and 38.3 percent among Saudi university female medical students, according to another report by Alsheikh [3]. According to the World Health Organization, 2 billion people are anemic worldwide, with iron deficiency accounting for half of all

anemia cases. Iron deficiency is the most common micronutrient deficiency in the world [4, 17]
Owaidah et al. [18] described regional variation in the prevalence of iron deficiency and IDA and reported highest prevalence of iron deficiency in the Makkah region. We could not assess the iron deficiency status in our patients wherein IDA appears to be highly prevalent. The overall anemia prevalence reported by AlAssaf [19] was 21% in females and 2.3% in males, whereas AlQuaiz et al. [17] reported anemia prevalence of 40% in women of reproductive age group in Riyadh. The only study reporting low prevalence of 12.5% was done in Tabuk in female university students in the age group of 19–25 years [1]. Majority of the studies conducted in Saudi Arabia have included selected population groups like children below the age of 5, school-going children, young adults/adolescents, pregnant women, and women in reproductive age group. [1, 4, 17, 20–23]. There are regional variations of anemia prevalence in Saudi Arabia within a specific group. Very few studies are conducted in the general population particularly in adults and the elderly [24, 25].
Numerous risk factors for the development of IDA in Saudi women of reproductive age have been identified [4]. Dietary habits, menorrhagia, a history of NSAID use, and a personal or family history of IDA are all risk factors [16, 17, 23, 25]. There is compelling evidence for a negative link between limited meat consumption and an increased risk of developing IDA [3]. As observed in earlier studies, irregular meals and skipping meals, particularly skipping breakfast, are risk factors for IDA [4]. Regular breakfast consumption has an effect on the prevalence of anemia [23]. Vitamin C has been shown to be an effective booster of iron absorption in nonheme meals, and citrus fruits are high in vitamin C [1]. Numerous studies indicate that a family history of genetic disorders is highly associated with IDA, and additional research is needed to confirm this [23]. Another factor for the high incidence is that the Saudi population consumes fewer multivitamin and mineral supplements than many other countries [26]. Microcytic anemia is more prevalent in females due to malnutrition, increased blood loss associated with pregnancy and menstruation, and a deficiency of iron absorption, whereas normocytic anemia is more common in males due to blood loss and chronic disorders [6]. Our results are in agreement with other studies. In our study, the prevalence of anemia in the elderly was 11.68 percent, which is consistent with a report by Alsaeed, who found that the prevalence of anemia in the elderly (>60 years) was 12.9 percent [25]. Males had increased prevalence of anemia with age in our study, whereas females had elevated prevalence in reproductive age groups and a continuous decline in anemia prevalence from the 5th to the 9th decades. Interestingly, normocytic anemia was more widespread in the fifth to ninth decades, demonstrating that anemia is caused by more than iron shortage. Macrocytic anemia was the least reported kind of anemia, accounting for fewer than 2% of cases, which is consistent with data from another Saudi Arabian investigation [13].
The cause of anemia in the senior population must be determined, and fresh studies must be conducted to investigate it. Consumption of tea, which contains a high concentration of polyphenols, has been linked to anemia in the elderly. Polyphenols block nonheme iron absorption. Tea drinking is a widespread ritual in Saudi Arabia and is typically drunk before and after meals [1, 22]. According to a study conducted in China, the high prevalence of anemia among the middle-aged population and elderly was caused by factors such as insufficient consumption of citrus fruits, reduced consumption of red meat, eggs, vegetables, and dairy, and excessive consumption of cereals, cooking oil, and salt, all of which were prevalent among the middle-aged and elderly population in China [16]. Another element to examine is the drastic shift in the Saudi population’s food habits from the traditional diet of dates, milk, rice, fresh vegetables, and seafood to junk foods and fewer green vegetables and fruits [20]. Other well-established risk factors for anemia include obesity and malnutrition [20, 27]. Obesity and overweight are considered chronic inflammatory processes and hence play a role in the development of anemia [27]. Anemia is a prevalent disorder among the elderly, and it is connected with an increased risk of death, disability, and impaired physical performance [25]. Numerous factors such as ethnic origin, smoking status, dietary inadequacy, and altitude of residence all influence a person’s red cell characteristics, and early detection of anemia in the elderly is critical for rapid intervention and management. The symptoms of anemia are not always obvious in the elderly, and efforts should be taken to determine the most likely cause of anemia. Folate, vitamin B12, serum ferritin, and serum erythropoietin levels should be determined. Additionally, Saudi Arabia has high prevalence of risk factors such as

obesity and an unhealthy lifestyle [20].

The World Health Assembly (WHA) has designated anemia reduction as a global dietary priority for 2025 [15]. There is a dearth of research documenting regional progress toward reducing anemia burden and the techniques and interventions being adopted. The trend in anemia prevalence over a ten-year period does not indicate a major decline, and anemia prevalence has remained stable in Saudi Arabia over the last decade [15]. Low and below-average public awareness initiatives can be blamed for the nation's failing health [22]. Saudi Arabia should take a multisectoral, community-based strategy to prevent and control anemia. Along with dietary inadequacies, nonnutritional causes of anemia such as acute and chronic parasite infections and genetic illnesses such as thalassemia, G6PD deficiency, and sickle cell trait must be addressed [15].

4.1. Limitations

Our study has some limitations. We included patients who visited a hospital, which may have inflated the numbers, but we excluded hospitalized patients. However, our findings are consistent with those of other research conducted in Saudi Arabia.

5. Conclusion

Our study showed high prevalence of anemia among the patients attending outpatient departments in a specialist hospital. Females have high prevalence of anemia when compared to male population. Microcytic anemia was the most common anemia type among females and was prevalent in the 15–49 age group considered as the reproductive age group, whereas normocytic anemia was more common among the male gender. Anemia of mild and moderate severity was predominant in both genders, although severe anemia showed higher prevalence in females as compared to males. The authorities need to address the problem of prevention and reduction in anemia prevalence in Saudi Arabia by taking effective measures and interventions.

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A Retrospective Study Using Mentzer Index for Prevalence of Iron Deficiency Anemia among Infants Visiting Maternal Centers at the Age of One Year

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ABSTRAK (ENGLISH)

Anemia, defined as a hemoglobin level two standard deviations below the mean for age, is prevalent in infants and children worldwide. Characterizing anemia as microcytic and normocytic depends on the mean corpuscular volume (MCV), which is an important parameter in differentiating many types of anemia. Microcytic anemia due to iron deficiency is the most common type of anemia in children. In this study, we aimed to assess the Mentzer index used by the Ministry of Health (MOH) in Palestine as a useful tool in differentiating between iron deficiency anemia (IDA) and thalassemia. We assessed for the prevalence of IDA among infants at the age of one year visiting the mother centers from seven West Bank provinces in Palestine. Medical records and hematology laboratory data of 3262 infants were retrospectively analyzed from the years of 2018 to 2020. The Mentzer index applied to all population by dividing mean corpuscular volume (MCV, in fL) by the red blood cell count (RBC, in millions per microliter). A corrected Mentzer index was further calculated among anemic infants to include only microcytic (MCV with less than 72 fl) and hypochromic (mean corpuscular hemoglobin concentration (MCHC) with less than 32 g/L) indices. Mentzer

index calculations for the whole population showed that 29.1% were anemic (hemoglobin (HGB) less than 11 g/dl): 21.1% had mild anemia, 7.6% had moderate anemia, while 0.2% had severe anemia. The corrected Mentzer index calculations showed a prevalence of 5.9% and 3.2% among IDA and thalassemia infants, respectively. Severity of anemia was correlated with low body weight and infants born through cesarean mother birth with no interference with gender influence. CBC indices of RBC count, HGB, MCV, and mean corpuscular hemoglobin (MCH) showed a significant difference (p values <0.05) between IDA and thalassemia infants' populations following the corrected Mentzer index. With the corrected Mentzer index, we introduced a new CBC index among infants at the age of 1 year in Palestine. These lab references could aid in differentiating IDA and thalassemia among the population and improve initial diagnosis screenings. The Mentzer index calculation for the whole population did not necessarily include cases of IDA, and therefore, it is recommended to comprise microcytic and hypochromic anemia indices prior to performing the Mentzer index.

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1. Introduction

Worldwide, anemia is a major public health problem and affects up to one-half of children younger than five years [1–5]. Anemia in childhood is defined as a hemoglobin (HGB) concentration below cutoff levels established by the World Health Organization (WHO) less than 11 g/dl in children aged 6–59 months [6]. Microcytic iron deficiency anemia (IDA) is a common cause of childhood anemia, whereas macrocytic anemia is rare in children. IDA in infants between 6 and 12 months can be caused by getting less than the recommended daily amounts of iron. The recommended daily amounts of iron will depend on the child age and sex. From birth to six months, the recommended daily amounts of iron uptake in milligram (mg) is 0.27, and this amount is increased to 11 [7]. A diet that does not have enough iron is the most common cause. During periods of rapid growth, even more iron is needed [8]. Iron deficiency can be grouped into three categories according to severity: (1) biochemical iron deficiency with normal erythropoiesis, (2) biochemical iron deficiency plus iron-limited erythropoiesis but without anemia, and (3) biochemical iron deficiency with IDA9. A low serum ferritin and a low serum iron can identify biochemical iron deficiency. Iron-limited erythropoiesis can be recognized by a fall in both reticulocyte HGB content and mean corpuscular volume, without a fall in HGB or hematocrit (HCT) [9, 10].

Most infants and children with mild anemia do not exhibit overt clinical signs and symptoms. Initial evaluation should include a thorough history, such as questions to determine prematurity, low birth weight, diet, chronic diseases, family history of anemia, and ethnic background [11, 12]. A complete blood count is the most common initial diagnostic test used to evaluate for anemia, and it allows differentiating microcytic, normocytic, and macrocytic anemia based on the mean corpuscular volume [13]. In the current study, we assessed for the prevalence of IDA among children visiting mother care centers at one year of age using the Mentzer index.

2. Patients and Methods

2.1. Sampling

In this study, medical records of 3262 infants, aged 12 months, were obtained from seven mother centers in the West Bank (Palestine) provinces of (Nablus, Qalqilya, Tulkarem, Jenin, Ramallah, Bethlehem, and Hebron). Data were screened for IDA between the years of 2018 and 2020. 466 cases were randomly obtained retrospectively from each province. The data were collected through a systematic sample by each year and included RBC count, HGB, HCT, MCV, body weight, and type of delivery. The ethical committee of institutional review board (IRB) provided approval. Data obtained from each patient were summarized at the centers and were handled discretely. Names of the patients were kept anonymous.

2.2. The Mentzer Index

The Mentzer index was used in differentiating IDA from beta thalassemia [14]. The index depends on two parameters included from the complete blood count. If the quotient of the mean corpuscular volume (MCV, in fL) divided by the red blood cell count (RBC, in millions per microliter) is shown to be less than 13, it is likely that the

patient could be thalassemic, while if the result is greater than 13, then the patient is most probably with IDA.

2.3. Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC) Calculations

MCH and MCHC were calculated from existing data for additional evaluation of IDA as hypochromic anemia: MCH = (hematocrit) HCT (%) × 10/RBC count (10–12/L) and MCHC = Hb (g/dL) × 100/HCT (g/dL).

2.4. Statistical Analysis

Data are shown as means ± SEM, unless stated otherwise. Statistical differences were analyzed between the IDA and thalassemia populations of the CBC indices using either the 2-tailed unpaired Student *t*-test (for comparison between two groups) or one-way analysis of variance (one-way ANOVA with Newman-Keuls posttests among multiple groups) using GraphPad Prism 5.0 (GraphPad software, La Jolla, CA). The *t*-test of p value below 0.05 was considered significant.

3. Results

3.1. Sample Characterization

Blood testing for infants agedone year is a mandatory procedure performed at the Ministry of Health (MOH). In the current study, we aimed to assess the overall prevalence of anemia in our sample population. Infants' data were stratified according to HGB levels; HGB levels under 11 g/dl were considered anemia (10 to 10.9 g/dl as mild anemia, 7 to 9.9 g/dl as moderate anemia, and less than 7 g/dl reflected severe anemia). Infants with HGB levels above 11 g/dl were nonanemic. Figure 1(a) displays that 29.1% of the infants were anemic (HGB less than 11 g/dl): 21.1% had mild anemia, 7.6% had moderate anemia, while 0.2% had severe anemia. Figure 1(b) displays the gender of the population among anemic infants, showing that 52% were females while 48% were males. Next, correlation of anemia severities with the total body weight ± SD of the infants was performed. Figure 1(c) shows inverse correlation between body weight and anemia severity among infants; significant results of $p<0.05$ were obtained between the groups. Furthermore, attempt to relate type of birth recorded in infants' files with anemia was studied. Many studies demonstrated an association between cesarean delivery and anemia in infants and children [15]. In this study, the association of type of birth (normal vs. cesarean (C-section)) with the prevalence of anemia was assessed. Figure 1(d) shows distribution of mothers' type of birth. Normal birth type was 77% and showed to be dominating the distribution among the nonanemic population (data not shown). Moreover, normal birth type distributions were reduced in the anemic population to 62% in favor of the C-section types. Average of HGB level in the C-section type was 10.2 ± 0.11 g/dl as compared to 10.4 ± 0.18 g/dl in the normal birth types (Figure 1(e), $p=0.012$).Additional CBC indices were included for better assessing anemia among infants' population. Table 1 shows infants' population grouped according to normal and low levels of MCV, MCH, and MCHC. Of the population, 38.6%, 48.6%, and 18.2% had low MCV, MCH, and MCHC, respectively.

[figures omitted; refer to PDF]

Table 1

Infant population stratified according to CBC indices of MCV, MCH and MCHC.

Values (%)	MCV (72.7–86.5 fl)	MCH (24.1–29.4 pg)	MCHC (32.4–35.3 (g/dl)
Low	38.6	48.6	18.2
Normal	61.4	51.4	81.2

3.2. Prevalence of IDA and Thalassemia by Mentzer Index

In an attempt to calculate IDA prevalence in our all-infants population, the Mentzer index was applied; the index was used in mother centers of the MOH of Palestine, as indicated in methods. Surprisingly, around 90% of the total population exhibit a Mentzer index of >13 while 10% showed <13, indicating the overall prevalence of IDA and thalassemia, respectively (Table 2). In the USA, recent surveys documented that the prevalence of IDA in children aged one to five years is estimated to be 1% to 2%14. Therefore, obtained data revealed a high prevalence of IDA

among Palestinian infants' population. In order to better interpret these data, the Mentzer index was calculated in the anemic vs. nonanemic population. Table 2 displays the anemic population demonstrating 83.2% of the population with Mentzer index >13 while 16.8% had Mentzer index <13. Moreover, 93.1% of the nonanemic population showed a Mentzer index of >13 and 6.9% had Mentzer index <13 (Table 2).

Table 2

Mentzer index in anemia and non-anemic populations. Mentzer index among all population, anemic population, non-anemic population and microcytic and hypochromic population.

Mentzer index	All population (%)	Anemic population (Hb	N (%)on-anemic population (Hb >11 g/dl)	Microcytic hypochromic population (MCV
>13	90	82.3	93.1	5.90
<13	10	16.8	6.9	3.20

The above results reveal a high prevalence of IDA and thalassemia cases among the whole population whether they are anemic or nonanemic. In addition, these data indicate that HGB above 11 g/dl does not necessarily exclude cases IDA or thalassemia as indicated by Mentzer index. Data showed a high IDA prevalence among Palestinian infants with the use of Mentzer index. Moreover, the Mentzer index used by MOH mother centers showed surprising data of 16.8% of thalassemia infants, of which infants could be either carrier or diseased. These results, altogether, could raise concerns on using the Mentzer index as a sole indicator for initial screening and emphasize the need to include additional CBC indices that might help improving screening outcome.

3.3. Prevalence of IDA and Thalassemia by Using "Corrected Mentzer Index" and a New Generated CBC Reference Range

The classical diagnosis of IDA and thalassemia should include CBC indices of MCV, MCH, and MCHC. Therefore, from the infants' records, we were able to calculate MCH [HCT (%) × 10/RBC count (10–12/L)] and MCHC [Hb (g/dL) × 100/HCT (%)]. IDA and thalassemia both are classified as microcytic hypochromic anemia [16] with HGB, MCV, MCH, and MCHC relatively low in favor of thalassemia. Therefore, we reapplied a "corrected Mentzer index" and included infants exhibiting "microcytic hypochromic anemia" using following cutoff indices: HGB less than 11 g/dl (normal values 11–14.1 g/dl), MCV less than 72 fl (normal values 72–84 fl), MCH less than 25 (normal values 25–29 pg), and MCHC less than 32 (32–36 g/dl). Table 3 displays CBC indices of the microcytic and hypochromic infants' population following the "corrected Mentzer index." Calculated results of the "corrected Mentzer index" of the prevalence of IDA and thalassemia are summarized in Table 2 showing 5.90% and 3.20 %, respectively. Later on, CBC indices of RBC count, HCT, MCV, MCH, and MCHC were assessed in both infants' populations. Table 3 summarizes averages of CBC indices in infants at the age of 1 year with microcytic and hypochromic anemia according to the "corrected Mentzer index". Following the use of "corrected Mentzer index," newly generated data were obtained and this included, for the first time, a new CBC reference range differentiating IDA and thalassemia that could be a useful initial screening for assessing anemia among infants at age 1 year.

Table 3

CBC indices among infants of IDA and thalassemia calculated by Mentzer index and applied on the classified microcytic and hypochromic anemia.

CBC indices	Thalassemia	IDA	P value
RBC count (10^6/ml)	5.42 ± 0.46	4.9 ± 0.2	P=0.0001

HGB (g/dl)	9.5±1.5	10.2±0.7	p=0.03
HCT (%)	33.1±3.3	33.7±1.8	P=ns
MCV (fl)	61.1±4.1	69.01±2.2	P=0.02
MCH (pg)	18.1±2.8	20.7±1.4	P=0.04
MCHC (g/dl)	29.7±2.2	30.2±1.7	P=ns

4. Discussion

Anemia is a global public health concern [1–5]. The American Academy of Pediatrics (AAP) and the World Health Organization (WHO) recommend universal screening for anemia at one year of age 14. The recommended daily amount of iron for infants from birth to 6 months is 0.27 mg, and these requirements increase to 11 mg from the age of 7 months to 1 year [7]. Infants between 6 and 12 months demonstrated increased risk for iron deficiency, especially if they are fed with breast milk or using milk formula that is not fortified with iron. The iron that full-term infants have stored in their bodies is used up in the first 4 to 6 months of life. Breastfed babies who do not get enough iron should be given iron drops prescribed by their doctor [6].

Most infants and children with mild anemia do not exhibit overt clinical signs and symptoms [17]; this could mask initial diagnosis, thereby, preventing anemia consequences if not treated. Prevalence of IDA among the infants' populations could be attributed to inadequate dietary iron intake, feeding problems and noncompliance to treatment with no-follow up program, all of which demand an effective assessments strategy for minimizing IDA cases [1, 18]. In Palestine, mother centers and 1-year-old infants are screened for IDA and thalassemia through the Mentzer index. The Mentzer index was used in differentiating IDA from beta thalassemia [14]. The principle involved is as follows: in iron deficiency, the marrow cannot produce as many RBCs and they are small (microcytic), so both the RBC count and the MCV will be low, and as a result, the index will be greater than 13. Conversely, in thalassemia, which is a disorder of globin synthesis, the number of RBCs produced is normal, but the cells are smaller and more fragile [6, 19]. Hence, the RBC count is normal, but the MCV is low, so the index will be less than 13. Therefore, by using this index, the study aimed to evaluate the prevalence of IDA among children visiting mother care centers at one year of age in 7 major centers all across Palestine (West Bank and excluding Gaza strip). In these centers, gender of infants was recorded together with the type of birth of mothers (natural or C-section). Initial evaluation of family history, questions to determine prematurity, low birth weight, diet, chronic diseases, family history of anemia, and ethnic background was neither included nor registered. Concerning CBC indices, RBC, HGB, HCT, and MCV were obtained. Further calculations were made to calculate the MCH and MCHC, as indicated in the methods section.

Because of high prevalence of IDA and thalassemia among the anemic population of HGB levels above 11 g/dl, using the Mentzer index for the whole population could lack accuracy and might raise some concerns particularly in having false cases. Applying the Mentzer index among the nonanemic infants' population indicated existence of IDA and thalassemia cases that clearly reflects its noneffectiveness in assessing IDA and thalassemia among the general population. Therefore, attempts were made to reapply the Mentzer index on the infants' population exhibiting anemia of microcytic (low MCV) and hypochromic (low MCH and MCHC through manual calculations) indices (corrected Mentzer index). In Palestine, the prevalence of IDA is 5.9%, and this is 5-times higher than that in 1-year-old infants in the USA [13]. More than 40 mathematical indices have been proposed in the hematological literature for discriminating between IDA and thalassemia traits in subjects with microcytic RBCs. None of these discriminant indices is 100% sensitive and specific, and the ranking of the discriminant indices is not consistent [20]. The Mentzer index was used by mother centers of the MOH in Palestine, and the aim of this brief report was to better assess IDA between our populations.

5. Limitations and Conclusions

Although the current study showed no documented follow-up program for infants, where mothers of infants are asked to visit a family doctor for further evaluation and iron therapy, no evidence of visiting a family doctor or hematologist is known. Therefore, this report recommends a policy for follow-up to infants showing IDA and thalassemia through performing hemoglobin electrophoresis, blood film, and serum iron profile, including ferritin. Moreover, the study difficulty was gaining access to a list of a larger population, time, costs, and that bias can still occur under certain circumstances, especially that more data collection was influenced with COVID-19 epidemic restrictions. The study introduced new CBC indices among infants at the age of 1 year in Palestine that could be used as reference ranges to better identify/differentiate IDA and thalassemia among the population.

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Glossary

Abbreviations

IDA:Iron deficiency anemia

HGB:Hemoglobin

MCV:Mean corpuscular volume

MCHC:Mean corpuscular hemoglobin concentration

MCH:Mean corpuscular hemoglobin

WHO:World Health Organization

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ABSTRAK (ENGLISH)

Background. Donated blood is an essential component of the management of many diseases, and hospital-based blood banks in Nigeria are saddled with the responsibility of provision of safe blood and coordination of its appropriate utilization for patient care. *Objective*. This study reviewed the extent to which the hospital blood transfusion service ensures adequate safe blood supply and utilization. *Materials/Methods*. This was a retrospective study of 2 years record of the blood bank service of Alex Ekwueme Federal University Teaching. Methods of donor blood procurement, transfusion transmissible infection status, the pattern of blood, and blood component usage across the hospital's clinical departments were evaluated. Statistical analysis was conducted using IBM SPSS, and data were presented as percentages. Fisher's tests were used to test significance, and p value <0.05 is significant. *Results*. The highest proportion of donors was male family replacement donors aged 26–35 years (3634 (39.68%)) while total voluntary donors were 315 (2.65%). Hepatitis B had the highest seroprevalence 267 (2.22%) among blood-borne diseases screened. National Blood Transfusion Service (NBTS) supplied only 3 (0.03%) of total blood units used. The accident and emergency department had the highest proportion of persons who utilized whole blood; 4568 (99.96%). *Conclusion*. The hospital blood bank relies heavily on family replacement donors with little or no assistance from the National Blood Transfusion Service. Family replacement donors have the highest risk of TTIs, and hepatitis B infection has the highest prevalence. The high cost of blood component therapy increases the need for whole blood.

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1. Introduction

Blood transfusion is the most commonly performed procedure in healthcare facilities [1–3]. Demand for blood is high; blood donation rates are very low, especially in low- and middle-income countries in Africa. Transfusion medicine has evolved from a laboratory service to clinical care with a focus on blood safety and appropriate clinical use of blood. The imperative goal is to improve clinical outcomes and patient safety. However, despite compelling evidence and ongoing WHO policy drive, Blood transfusion safety in Nigeria has been challenged by a shortage of voluntary donors, poor infrastructure, high cost of blood components, and high prevalence of transfusion transmissible infections (TTIs) [4].

Transfused blood is a known risk for transmission of infectious diseases including hepatitis B, C, and HIV. The prevalence of hepatitis B infection among blood donors in Nigeria has been variable. A study reported the prevalence of HBV, HCV, syphilis, and HIV to be 4.1%, 3.6%, 3.1%, and 4.2% among donors while another study reported rates as high as 17% for hepatitis B seropositivity and as low as 0.45% for HIV [5–9].

Donorship rates for voluntarily donated blood are very low in Nigeria. The National Blood Transfusion Service, which is the agency responsible for safe blood supply in Nigeria is unable to meet more than 75% of the blood needs of the populace [10].

The effectiveness and safety of hospital blood transfusion services in our country with a low human development index are critical to healthcare delivery. This study seeks to define the extent to which the hospital blood transfusion service ensures adequate safe blood supply and utilization, at a tertiary hospital in southeast Nigeria.

1.1. Subjects, Materials, and Methods

This was a retrospective study conducted at the Department of Haematology at the Alex Ekwueme Federal

University Teaching Hospital, Abakaliki, Ebonyi State (AEFUTHA). Ethical approval was obtained from the Ethical and Research Committee of AEFUTHA (REC protocol no. 19/04/2021–10/06/2021). Records from the blood transfusion unit and hospital ward blood transfusion register from January 1, 2019, to December 31, 2020, were collated and analyzed to identify the methods of donor blood donation, demographic data (age and sex) of blood donors during the specified study period, the various categories of blood donors, the prevalence of TTI markers, and pattern of blood and blood component usage across the hospital's clinical departments.

No autologous donation was done during the study period. The sources of blood procurement are paid blood donors, voluntary donors, and family replacement donors. A paid blood donor offers a unit of blood for a pecuniary benefit by a contracted hospital vendor. A replacement blood donor is a family member or relative of a patient, donating a unit of blood to be used for a specific patient, while a voluntary blood donor is a member of the society who donates his or her blood without any inducement for use by a recipient not known to him or her. Commercially donated blood is supplied to the hospital blood bank by contracted vendors while blood from voluntary donors and replacement donors are collected in the hospital donor clinic after packed cell volume, blood group, and other eligibility criteria are determined. Thereafter, sera samples are tested for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C virus (HCV), human immunodeficiency virus (HIV) 1/2, and *Treponema pallidum* using commercially available immunochromatic based rapid kits. A single red line at position *C* (control) on the strip indicates a valid control. A test is positive if two transverse bands (*T*=test and *C*=control) are seen and negative when only the one band at control (*C*) is seen. Those who test positive are disqualified. Blood (450 ml) is usually collected into a bag containing 63 ml citrate phosphate dextrose with adenine (CPDA) using the standard guidelines for routine phlebotomy and stored at 2–8°C as whole blood or separated into components (fresh plasma, red cell concentrate, or platelet-rich plasma) using the cold centrifuge machine. Donors for platelet concentrate have their predonation platelet count measured (predonation platelet count of at least 200,00/μl required) and blood group determined since platelet concentrate transfusion is blood group-specific and prepared only on demand due to cost. The Haemonetics MCS apheresis machine is used for platelet concentrate harvest from the donors. They are stored in the platelet agitator. Whole blood supplied by vendors (paid donors) are also tested for, hepatitis B, C, *Treponema pallidium*, and HIV 1 and 2 after supply and if found to be negative for all fours tests, they are then stored in the blood bank refrigerator for use.

Statistical analysis was conducted using IBM SPSS, and data were presented as percentages. Fisher's tests used to test significance, and p value <0.05 is significant.

2. Results

Table 1 shows the age and sex distribution of persons who donated blood during the study period. The majority of blood donors were males (12,268 (97.11%)) amongst which those aged 26 to 35 years were the highest proportion (4,729 (38.47%)).

Table 1

Age and sex distribution of persons who donated blood during the study period.

Age groups	Male *n* (%)	Female *n* (%)	Total *n* (%)
18–25 years	3,905 (31.83)	148 (40.66)	4,053 (31.90)
26–35 years	4,729 (38.47)	156 (42.86)	4,885 (38.61)
36–45 years	3,041 (24.79)	48 (13.19)	3,089 (24.60)
46–55 years	552 (4.50)	10 (2.75)	562 (4.54)

56–65 years	38 (0.31)	1 (0.27)	39 (0.31)
>65 years	3 (0.024)	1 (0.27)	4 (0.03)
Total	12,268 (97.11)	364 (2.94)	12,632 (100.0)

Table 2 shows the age and sex distribution of study donors across the categories of blood donation. The highest proportion of donors were male family replacement donors (3,634 (39.68%)) and female replacement donors (143 (43.86%)) aged 26 to 35 years. Voluntary donors contributed 315 (2.65%) of all the categories of blood donors.

Table 2

Age and sex distribution of donors across the categories of blood donation.

Age groups	Voluntary donors		Family replacement donors		Paid donors	
	Male (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)
18–25 years	84 (30.32)	16 (42.11)	2,580 (28.17)	122 (37.42)	1,591 (56.11)	0 (0.0)
26–35 years	113 (40.79)	17 (44.74)	3,634 (39.68)	143 (43.87)	1,036 (36.54)	0 (0.0)
36–45 years	69 (24.91)	4 (10.52)	2,483 (27.11)	46 (14.11)	196 (6.91)	0 (0.0)
46–55 years	10 (3.61)	1 (2.63)	429 (4.68)	13 (3.98)	12 (0.42)	0 (0.0)
56–65 years	0 (0.0)	0 (0.0)	28 (0.30)	1 (0.30)	0 (0.0)	0 (0.0)
>65 years	1 (0.3)	0 (0.0)	2 (0.02)	1 (0.30)	0 (0.0)	0 (0.0)
Total	277 (2.2)	38 (0.3)	9,156 (72.4)	326 (2.7)	2,835 (22.44)	0 (0.0)

Family replacement donors had the highest number of rejection/deferral 358 (59.6%) while low haemoglobin was the commonest reason for rejection/deferral 444 (73.8%).

Table 3 shows the distribution of blood groups across persons who donated blood during the study period. The majority of donors were O Rh-positive (8,739 (73.1%)) followed by A Rh-positive (1,411 (11.8%)). Only one person had AB Rh-negative blood group.

Table 3

Distribution of blood group across persons who donated blood during the study period.

Blood group	Frequency	Percentage

A Rh−	38	0.3
A Rh+	1,360	12.1
B Rh−	39	0.3
B Rh+	1,057	9.4
AB Rh−	1	0.0
AB Rh+	56	0.5
O Rh−	403	3.6
O Rh+	8,239	73.6
Total	11,193	

Table 4 shows the seroprevalence of blood-borne diseases among blood donors screened during the study period. Hepatitis B had the highest seroprevalence (267 (2.22%)) among blood-borne disease screened for p value <0.001. HIV had the lowest seroprevalence (101 (0.82%)). Amongst the different categories of donors, the hepatitis B, C, HIV, and syphilis seroprevalence was highest among family replacement donors (2.52%, 2.18%, 0.95%, and 2.22%, respectively) while voluntary donors had the lowest. The relative risk of infection transmission was 2.56 and 1.68 for HIV and hepatitis B infections, respectively.

Table 4

Seroprevalence of blood-borne diseases among persons screened during the study period.

TTI	Donor group	Positive (%)	Negative (%)	Total *N* (%)	Chi square	p value	Relative risk
	VNRD	1 (0.37)	268 (99.63)	269 (100.0)			1
HIV	FRD	87 (0.95)	9037 (99.05)	9124 (100.0)	4.952	0.084	2.56
PAID	13 (0.49)	2625 (99.51)	2638 (100.0)			1.33	Total
101 (0.82)	11930 (99.18)	12031 (100.0)				VNRD	4 (1.50)
263 (98.50)	267 (100.0)			1	HBV	FRD	230 (2.52)
8894 (97.48)	9124 (100.0)	14.940	0.001	1.68	PAID	33 (1.25)	2602 (98.75)

2635 (100.0)			0.84	Total	267 (2.22)	11759 (97.78)	12026 (100.0)
			VNRD	8 (3.0)	259 (97.0)	267 (100.0)	
	1	HCV	FRD	199 (2.18)	8925 (97.82)	9124 (100.0)	9.9392
0.009	0.73	PAID	33 (1.26)	2595 (98.74)	2628 (100.0)		
0.42	Total	240 (2.00)	11779 (98.0)	12019 (100.0)			
VNRD	5 (1.87)	262 (98.13)	267 (100.0)			1	Syphilis
FRD	203 (2.22)	8921 (97.78)	9124 (100.0)	19.473	0.00006	1.19	PAID
22 (0.84)	2598 (99.16)	2620 (100.0)			0.45	Total	230 (1.91)

Table 5 shows source/site of blood donation (hospital, private lab, NBTS, and others).

Table 5

Site of blood donation/procurement.

Source of blood	Frequency	Percentage
Hospital blood bank (VNR and FR)	8,655	74.7
Paid	2,923	25.2
NBTS*	3	0.03
Total	11,581	100.0

*National Blood Transfusion Service.

Hospital screening and blood donation (voluntary, family replacement, and paid) constituted the largest source of blood during the study period (8,655 (74.7%)). Vendor-sourced commercial blood accounted for 2,537 (21.9%). NBTS contributed only 3 (0.03%).

Table 6 shows the pattern of usage of blood and blood products across clinical departments.

Table 6

Pattern of usage of blood and blood components across clinical departments.

Blood component	O &G (%)	Paed (%)	Surgery (%)	A &E (%)	Medicine (%)	Haematology (%)

Whole blood	2,479 (99.67)	481 (94.31)	1,041 (98.49)	4,568 (99.96)	1,150 (94.10)	1,710 (98.55)
Red cell concentrate	1 (0.04)	7 (1.37)	4 (0.37)	1 (0.02)	32 (2.61)	3 (0.17)
Platelets	0 (0.00)	9 (1.76)	1 (0.09)	1 (0.02)	28 (2.29)	12 (0.69)
Fresh Plasma	7 (0.28)	13 (2.54)	11 (1.04)	0 (0.00)	12 (0.98)	10 (0.57)
Total	2,487 (21.47)	510 (4.40)	1,057 (9.12)	4,570 (39.46)	1,222 (10.55)	1,735 (14.98)

A total of 11,581 blood units were used during the period under study. The accident and emergency department had the highest proportion of persons who utilized total whole blood (4,568; 99.96%) while internal medicine used the highest number of platelets and fresh frozen plasma with haematology department (28; 2.29% and 12; 0.98%) and (12; 0.69% and 10; 0.57%), respectively.

3. Discussion

Voluntary nonremunerated blood ensures safety, quality, availability, and accessibility of blood transfusion. Our study revealed that family replacement and commercial donors were the major sources of blood during the study period with voluntary unpaid donors contributing only 2.65%. These results are comparable to those obtained in other reports, where family replacement donors and commercial donors made up 99% [11] and 95.3% [12], respectively of donated blood in the hospital blood bank. Family replacement donors are not the best source of blood since these donors are usually under pressure to give blood to save a loved one even when they are not eligible on account of being potential transmitters of TTIs or their health is at risk. A more appalling twist to family replacement blood donation is the fear that many of the so-called family replacement donors may not be true relatives but commercial donors co-opted to act as family replacements [13]. The lack of effective community blood drive programmes could account for the low level of voluntarily donated blood and a functional donor clinic can facilitate the conversion of the huge family replacement donor base to voluntary donors. Misconceptions, lack of information, and a high rate of unemployment have also encouraged commercial blood donation to thrive [14, 15]. Demographic information of blood donors is important for drafting and monitoring recruitment strategies [16]. In Africa, males constitute the majority of blood donors with women constituting less than 30% of the donor population [17]. In keeping with our study also, females accounted for only 3.99% of blood donors in our blood bank and the majority were family replacement donors. Our findings differ starkly from those obtained from studies in developed countries [18, 19] where females accounted for as high as 40% to 55% of the blood donor population despite the prevailing barriers including pregnancy, breastfeeding, menstrual blood loss, low blood haemoglobin concentration, and greater susceptibility to vasovagal reactions. Lack of access to education, cultural beliefs, and economic deprivation are further barriers to female participation in blood donation in our locality. Deferral rates due to anaemia are high in females, especially in developing countries [20]. In our environment, a high incidence of malarial infections in the general population and iron deficiency anaemia is notable [21].

Transfusion transmissible infections pose the greatest threats to blood transfusion safety [22]. Our study revealed that the prevalence of HIV, hepatitis C, and syphilis infections in our family replacement donors was higher than that of donations in low-income countries as reported by the WHO [3]. Even though the prevalence for hepatitis B among the different categories of donors was slightly lower than reported by the WHO, family replacement donors has the highest prevalence rate of 2.52 with a 1.68 risk of being infected. A similar prevalence of hepatitis B infection has been found in another study [23]. The commercial and voluntary donors had lower seroactivity and relative risk of transmission of blood-borne diseases. Family replacement donors may have a higher rate of seroactivity of the TTIs since they constitute the greater proportion of total donors assessed. They are usually under immense pressure to donate blood to save the life of someone known to them in emergent situations and are likely to evade divulging information connected to a risky lifestyle that might lead to denying them eligibility to donate. This is at variance with

voluntary donors who tend to be repeat donors for altruistic reasons and so are aware and maintain a lifestyle that makes them always eligible. The low prevalence of TTIs among commercial donors may be due to their understanding that their source of income from blood donation may be cut off if they engage in high-risk behaviors that may make them ineligible to donate blood in the future. This disturbing concept has arisen due to poverty and unemployment and requires urgent steps to curb it including proper education and job creation.

Blood group and rhesus typing are routinely determined in blood donors as they are clinically important in haemolytic transfusion reactions The predominant blood type in our study was type O and the least common was type AB, consistent with other studies in Nigeria [24]. In Eastern and Southern African countries, blood group O dominated the populace, while in Pakistan and some regions in India on the Asian continent, blood group B dominated [25–27]. In addition to being the most common blood group in our population, the high rate of utilization of blood group O is seen where there is an inadequate supply of donor blood, particularly in emergencies when it is commonly used as universal donor units for transfusion to A, B, and AB recipients, This is predicated on the premise that blood group O red cells lack A and B antigens on their cell membrane surfaces, despite the risk of the presence of anti-A and anti-B haemolysins in blood type O donors [28].

Contrary to the report by Enosolease et al. [12], our study revealed that blood utilization was more than supplied by the blood bank. This shortage necessitated patients resorting to blood procurement from peripheral laboratories when the hospital blood bank had none. In concordance to the study by Okocha et al. [11], the Accident and Emergency department had the highest rate of utilization of whole blood followed by the obstetrics and gynaecology department. The high blood use by the accident and emergency department is probably a result of the increased requirement of whole blood for emergent resuscitation due to blood loss. The rising incidence of road traffic accidents in our environment is culpable.

More than 98% of blood used during the study period was whole blood. This contributed to increasing our blood needs. The use of whole blood has continued in resource-limited low- and medium-income countries despite the benefits of component therapy. Component therapy allows several patients to benefit from one unit of donated whole blood thereby maximising its use. Most times fresh whole blood transfusion is a quick and cheap fix for patients requiring platelets or coagulation factors only. This is associated with alloimmunization, overload, and poor treatment outcomes. Transfusion of whole blood rather than the indicated component is a failure of stewardship of the scarce blood resource. From our study, the internal medicine department and the haematology unit had the highest utilization of blood components such as packed red cells and platelets possibly due to the chronicity of diseases that affect distinct blood cell lines and so afford time for the patient to gather funds to procure the required blood component. Also, most haematological premalignant and malignant diseases are associated with dangerously low blood counts that require component therapy to support treatment. The low use of blood component therapy is due to the high cost and lack of infrastructure in our environment [12].

Hospital-based blood donation by family replacement and voluntary donors made up the largest contribution to donor blood used in the hospital during the study period while the National Blood Transfusion Service (NBTS) provided only three units of blood. NBTS is saddled with the responsibility to provide safe, quality blood and blood components in a cost-effective manner and distribution to hospitals throughout the country. Currently, Nigeria needs an average of 1.8 million pints of blood annually to meet the blood transfusion needs of 200 million Nigerians, but only 500,000 units are collected annually by the NBTS, amounting to only 27.7% and leaving a deficit of 73.3%.10 Problems faced by the NBTS include inadequate policy enforcement and funding shortfalls which impact its ability to enlighten more people and increase donor recruitment. The funding challenge hinders activities such as media outreach, advocacy, and public awareness campaigns down to the community level which would have tackled the deeply rooted cultural myths and misconceptions on voluntary blood donation in the country. The gap created by the nonfunctional NBTS is filled by vendor-sourced blood which contributed about one-fifth of the total blood used during the study period reflecting the huge dependence on commercially sourced blood in addition to those who disguise as family replacement donors.

More action is urgently needed from policymakers and stakeholders in strengthening the capacity of the National

Blood Transfusion Service to ensure that more units of voluntarily donated blood are supplied to hospitals. Donor education of the populace especially targeting the youths is key to inculcating the right concept and culture of VNR blood donation. Hospital donor clinics to aggressively drive community outreaches, donor drive, and design programmes to encourage family replacement donors to become voluntary donors. Government and hospital managers should gear efforts toward the provision of equipment for component preparation and making it affordable. Also, TTI screening must step up to better and more sensitive screening techniques considering the large volume of blood required by patients.

3.1. Study Limitation

This is a retrospective study, and donors/recipients with incomplete data from the blood register were removed from the analysis. The data of most recipients' prehaemoglobin levels and diagnosis were missing and could be included as part of the study.

4. Conclusion

Blood donation deficit has been demonstrated in this study, and hospital transfusion services are still largely dependent on commercial donors and family replacement donors as the predominant source of blood and blood products utilized by the hospital. The utilization of whole blood was increased due to the nonaffordability of blood components. Moving forward, the National blood transfusion service must become proactive in using results of donor behaviour studies and implementation of actionable policies to improve safe blood supplies to the hospitals. Donor education of the populace especially targeting the youths is key to inculcating the right concept and culture of VNR blood donation. There is a great need for mass mobilization and retention of VNRD through effective evidence-based educational, cultural religious, and gender-based peculiarity intervention programmes and incentives. Hospital blood banks should have dedicated units saddled with this primary responsibility. Government and hospital managers should gear efforts toward the provision of equipment for component preparation and making it affordable. Also, TTI screening must step up to better and more sensitive screening techniques considering the large volume of blood required by patients and prevalence of TTIs.

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Elucidating the Correlation of D-Dimer Levels with COVID-19 Severity: A Scoping Review

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ABSTRAK (ENGLISH)

Aims. The review explores the findings of previous studies to elucidate the association between levels of D-dimer and COVID-19 severity and prognosis. In addition, we assessed the efficiency of anticoagulant therapies in reducing COVID-19 severity and improving the prognosis of the patients. *Materials and Methods*. A comprehensive literature review was conducted using MEDLINE/PubMed databases, Scopus, and Web of Science with the help of keywords “COVID-19,” “D-Dimer,” “Thrombosis,” “Fibrin network,” “Anticoagulant therapy,” “Inflammation,” and “disease severity.” Based on all these articles and clinical experience, a scoping review was constructed and the full texts of the articles that were retrieved were accessed. *Results*. A D-dimer is a complex protein molecule that is formed during plasmin-mediated degradation of the fibrin network. Thus, it serves as a marker of thrombotic activity. On the other hand, in addition to severe respiratory distress and reduction in pulmonary gas exchange, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also triggers prothrombotic changes in the infected individuals. The levels of D-dimer have been postulated to be positively associated with the degree of disease severity among COVID-19 patients. *Conclusions*. It has been postulated that D-dimer could potentially be used as a biomarker to predict the prognosis and outcome of COVID-19 patients at the time of admission to hospitals and facilitate more personalized and efficient clinical management that could significantly reduce the mortality rate of such patients and allow more rapid recovery.

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1. Introduction

The first case of coronavirus disease 2019 (COVID-19) was reported in December 2019 in the Wuhan province of China. After that, it quickly spread across 200 countries within a span of a few months. Global research efforts quickly identified the etiological agent of this disease to be a novel coronavirus. This novel coronavirus exhibited approximately 80% homology to SARS-CoV, which had earlier spread during 2002–2003 and was associated with acute respiratory distress syndrome (ARDS) and a high mortality rate [1]. The novel coronavirus was hence named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 or 2019-nCoV). Although this virus entered the human population via zoonotic transmission, its spread is mainly attributed to human-to-human transmission [2]. The World Health Organization (WHO) declared this outbreak a Public Health Emergency of International Concern by 30 th January 2020. Later, this outbreak was declared a global pandemic by 12th March 2020 [3].

The novel coronavirus primarily transmits via respiratory droplets. The angiotensin-converting enzyme 2 receptor present on the cell surfaces plays a key role in the invasion of the novel coronavirus [4]. Most of the COVID-19 patients are usually asymptomatic and do not require hospitalization. However, sometimes, after an incubation of 2–14 days, COVID-19 symptoms may emerge, including shortness of breath, fever, coughing, and pneumonia [5]. Previous studies have reported that some cases exhibit the development of severe pneumonia, leading to hypoxia and respiratory dysfunction. The most severe cases (less than 5% of the symptomatic cases) exhibit ARDS and multiple organ failure, along with several laboratory abnormalities, such as leukopenia, thrombocytopenia, hypercoagulative state, leukopenia, and elevated levels of D-dimer, which often warrant admission to the intensive care unit (ICU) [6, 7]. This review focuses on the potential of D-dimer as a biomarker to predict the disease severity of COVID-19 patients and their outcome. We also assessed the efficiency of anticoagulant therapies among such patients to reduce their disease severity and improve their prognosis.

2. Materials and Methods

A comprehensive literature review was conducted using MEDLINE/PubMed databases, Scopus, and Web of Science with the scope of the searches confined to English language sources. There was no time restriction

specified since the items on COVID-19 continue to accumulate on a regular basis. Priority was given to articles with a stronger evidence base, even though all types of articles were examined. The following keywords were employed: “COVID-19,” “D-Dimer,” “Thrombosis,” “Fibrin network,” “Anticoagulant therapy,” “Inflammation,” and “disease severity.” In general, we followed the guidelines for producing scoping reviews that were provided to us.

3. Result

3.1. D-Dimer Structure and Formation

A D-dimer is a complex protein molecule that is generated during plasmin-mediated cross-linked fibrin degradation. Figure 1 depicts the process of D-dimer formation in the form of a schematic illustration. As the D-dimer formation commences, the fibrin molecules are formed after the thrombin-mediated cleavage of fibrinogen, a soluble glycoprotein that is found in the plasma. Thrombin cleaves the polymerization site of a fibrinogen molecule, thereby exposing the site to bind with other fibrinogen or fibrin molecules. In this manner, several such cleaved fibrin molecules bind together in an overlapping fashion to form protofibrils [8]. The thrombin molecules remain bound to the fibrin molecules during their polymerization. At this point, thrombin simultaneously activates the fibrinogen-bound plasma factor XIII. The complex of the thrombin molecules, plasma factor XIII, and fibrin polymers together triggers the formation of factor XIIIa [9]. Plasma factor XIIIa is instrumental in the cross-linking of the fibrin molecules. In the next step, plasminogen interacts with the fibrin molecules, which leads to the formation of plasmin.

[figure omitted; refer to PDF]

The generated plasmin molecules, in turn, bind with the fibrin molecules and mediate degradation of the bound fibrin into products with different molecular weights, commonly known as fibrinogen degradation products (FDPs). Plasmin also mediates terminal degradation of the cross-linked fibrin molecules into soluble fragments that contain DDE fragments. A DDE fragment, simply put, is a D-dimer molecule that is noncovalently bound to fragment E. The plasmin molecule further breaks down the DDE fragment into DD and E fragments. The D-dimer (DD fragment + E fragment) is a soluble complex and circulates in the plasma until it is eliminated by the reticuloendothelial and renal pathways [9]. It is noteworthy that the half-life of D-dimer that circulates in the plasma is 8 h and can be detected in the blood only 2 h after the formation of a thrombus [10]. The formation of D-dimers only occurs during the generation and degradation of the cross-linked fibrin molecules, which takes place during coagulation and fibrinolytic events. Therefore, the D-dimer molecules serve as a direct marker of these events as well as an indirect marker of thrombotic activity.

There are three major steps of D-dimer formation:

(i) Fibrin monomers are generated after the degradation of a fibrinogen molecule by thrombin. The generated fibrin monomers then bind to other fibrin or fibrinogen molecules, which results in the formation of protofibrils. The dotted lines between the D-E domain and the D domain depict the noncovalent interactions that aid in maintaining the structural integrity of the protofibrils.

(ii) Simultaneously, thrombin activates the formation of plasma factor XIIIa that binds to the D-domains of the fibrin polymers via covalent interactions.

(iii) Then, fibrin degradation products (FDPs) are formed after the disrupting action of plasmin on multiple sites of fibrin, which, in turn, exposes the D-dimer antigen epitope. These FDPs are then further degraded, resulting in the formation of a terminal DDE complex [9].

3.2. Cross-Link between Thrombosis and Fibrinolytic Pathways

The fibrinolytic system is responsible for the prevention of the formation of fibrin thrombi. Such thrombi are mainly composed of fibrin polymers and, under normal circumstances, they are disrupted by the fibrinolytic system as soon as they are generated. Currently, such FDPs are the most widely used biomarkers of thrombosis. Several modulators play a key role in the promotion (such as tissue plasminogen activator and TPA) or prevention (such as thrombin activatable fibrinolysis inhibitor) of fibrin degradation. As abovementioned, the DDE fragment (D-dimer) only generates when plasma factor XIII degrades the fibrin polymers. Thus, this fragment holds great potential as a biomarker of fibrin degradation and coagulatory pathways and, in turn, thrombosis [11].

3.3. COVID-19 and Thrombosis

Since its emergence, several investigators around the globe have published a plethora of studies on the epidemiology of COVID-19. Although its transmittance rate is extremely high, it has a very low mortality rate of 2.3% [12]. A higher incidence of COVID-19 has been reported among individuals aged more than 65 years and less than 18 years, with a higher sequential organ failure assessment (SOFA) score, male gender, and several comorbidities, including diabetes, hypertension, and coronary heart disease [3]. In addition, several studies have also shown that a D-dimer level of more than 1 μg/mL to be a potential risk factor of COVID-19 [13]. The formation of thrombi has been reported in both the venules as well as the arterioles of COVID-19 patients at the time of hospitalization. It has been postulated that this observation could be attributed to the risk factors that contributed to the aggravation of COVID-19 in an individual, such as obesity, pregnancy, and comorbidities like diabetes mellitus, which often themselves participate in and trigger the formation of clots in the bloodstream [14, 15]. The formation of such thrombi and the resultant angiogenesis often give rise to impaired microcirculation in COVID-19 patients [16]. Previous studies on COVID-19 patients have shown that the novel coronavirus is often responsible for endothelial injury and cell membrane destruction. This, in turn, reduces the fibrinolytic activity of endothelial cells, which promotes the formation of thrombi [17].

It is noteworthy that the proinflammatory cytokines are involved in both inflammatory and coagulatory processes. Previous studies have shown that severe infection of novel coronavirus triggers severe inflammatory reactions, as indicated by the significant upregulation of proinflammatory cytokines [18]. The cytokine upregulation and coagulopathy observed in cases of severe novel coronavirus infection have been attributed to acute sepsis [19]. Furthermore, severe novel coronavirus infection often predisposes infected individuals to sepsis-induced coagulopathy and disseminated intravascular coagulation [20]. Recently, Maier et al. reported a significant association between novel coronavirus infection and an increase in the viscosity of the plasma of the infected individual [21]. Such an increase in plasma viscosity has been reported to be associated with an increase in SOFA scores. This finding indicated that hyperviscosity of the plasma could trigger both endothelial dysfunction as well as thrombosis. Blood viscosity is also affected by fibrinogen levels [22]. Previously, it has been reported that the fluidic state of the plasma is maintained only till thrombin is able to cleave about 25% to 30% of the plasma fibrinogen. This, in turn, facilitates efficient polymerization of fibrin monomers and promotes the activation of plasma factor XIII by thrombin [9]. It is demonstrated that COVID-19 patients also exhibited high plasma levels of fibrinogen [22].

4. Discussion

4.1. Association between Levels of D-Dimer and COVID-19

As stated above, the levels of D-dimer directly correlate with the rate of formation and degradation of plasmin. Hence, any pathological condition that upregulates the rate of plasmin generation and degradation would also increase the levels of D-dimer. Thus, the pathologies that promote chronic inflammation, such as rheumatoid arthritis, asthma, and cancer, also lead to an increase in the levels of D-dimer. It follows that infection of a novel coronavirus, which leads to upregulated inflammatory reactions among individuals, would also increase the levels of D-dimer. This is evident by the findings of several previous studies that showed that levels of D-dimer were significantly higher in COVID-19 patients, especially those who were either severely ill or had deceased [23, 24]. Some investigators have postulated that the upregulated levels of D-dimer in individuals with severe novel coronavirus infection might be associated with severe illness, higher rates of thrombotic activity, and higher mortality rates of such patients [14, 25].

In 2020, Guan et al. presented the results of a large retrospective study that indicated the correlation between abnormal levels of D-dimer and disease severity of the COVID-19 patients for the first time [26]. Setting a cut-off point of a D-dimer level of more than 0.5 mg/L, they reported that a significantly higher proportion of novel coronavirus infected individuals with severe illness exhibited abnormally high levels of D-dimer than those with only mild or moderate illness ($p=0.002$) [26]. Furthermore, Tang et al. reported that COVID-19 patients with a severe level of illness exhibited approximately 3.5 times higher levels of D-dimer compared to patients with only mild or moderate levels of illness [27]. Their results were corroborated by Wang et al., who reported approximately 2.5- and 5-times higher levels of D-dimer, respectively, in COVID-19 patients with a severe level of illness compared to

patients with only mild or moderate levels of illness [23, 24]. In line with these findings, Wang et al. also found that the levels of D-dimer in COVID-19 patients with severe illness were more than two times lower compared to the levels of D-dimer of deceased COVID-19 patients. Their results were supported by Tang et al., who demonstrated that COVID-19 patients with severe illness exhibited around four- and nine-times lower levels of D-dimer, respectively, compared to the levels of D-dimer of deceased COVID-19 patients [13, 27].

In a recent study, Lippi and Favaloro observed that the levels of D-dimer of the COVID-19 patients with a mild or moderate level of illness, that is, those who did not require ICU admission, were significantly lower than the levels of D-dimer of the patients with a severe level of illness, that is, those who required ICU admission [28]. In another study, Yao et al. demonstrated that COVID-19 patients who were categorized as suffering from a severe level of illness on the basis of their oxygenation index, lung CT scans, and corresponding clinical guidelines exhibited a significant association between their disease severity and levels of D-dimer [18]. Bilaloglu et al. conducted a multicentric study to examine the upregulation of levels of D-dimer in individuals who were hospitalized due to COVID-19 [29]. Their results indicated that, among the recruited patients, around 76% of the patients exhibited abnormally high levels of D-dimer during admission to the hospital, whereas around 86% of the patients exhibited abnormally high levels of D-dimer at any time during their hospitalization. Petrilli et al. reported that, at the time of admission to the hospital, the COVID-19 patients with abnormal levels of D-dimer exhibited poorer outcomes [30]. Around 43%, 20%, and 45% of the patients suffered from acute kidney injury, thrombosis, and critical illness, respectively. In addition, they conducted a multivariate analysis to identify the underlying factors that affected the outcomes of such patients and found that the levels of D-dimer were independently correlated with the patient's outcome. On the contrary, patients with normal levels of D-dimer exhibited higher odds of recovering without developing severe illness.

The novel coronavirus infection leads to upregulation of the inflammatory pathways. According to the results of several previous studies, the abnormal increment in the levels of D-dimer under inflammatory conditions indicates that the upregulation of inflammatory reactions and proinflammatory agents might be associated with the induction of the coagulatory pathways [31]. Hence, it follows that the coagulatory events in the COVID-19 patients might be triggered by the upregulated inflammatory reactions. This postulate was further strengthened by the findings of Bilian et al., who reported a significant correlation of the levels of D-dimer with the levels of hsCRP, a marker of inflammation, in COVID-19 patients [32]. In another study, Chen et al. showed how the levels of D-dimer could potentially be used as a marker to predict the inhospital mortality rate of COVID-19 patients [33]. Based on their results, they were able to determine a cut-off D-dimer value of more than 2.14 mg/L to predict the outcome of COVID-19 patients at the time of admission to the hospital. They reported that this cut-off value could be efficiently used to predict the rate of inhospital mortality with 88.2% sensitivity and 71.3% specificity. On the other hand, in their recent review, Zheng et al. reported that the levels of D-dimer of more than 0.5 mg/L indicated abnormally high blood coagulability of COVID-19 patients and were significantly correlated with poor outcomes of such patients [34]. Table 1 enlists some of the retrospective studies that demonstrated a significant correlation between levels of D-dimer and disease severity among COVID-19 patients [13, 27, 35–43].

Table 1

A list of some retrospective studies showing the significance of the association of D-dimer levels with disease severity among the COVID-19 patients [13, 27, 35, 36, 37, 38, 39, 40, 41, 42, 43].

	Study population	Observations
Han et al. 2020	Control vs. COVID-19 patients	COVID-19 patients exhibited significantly higher levels of both D-dimer and fibrinogen

Zhou et al. 2020	COVID-19 survivors vs. nonsurvivors	Patients with D-dimer level >1 μg/mL exhibited significantly (18 times) higher mortality than those with D-dimer level <1 μg/mL (p=0.0033)
Cui et al. 2020	COVID-19 patients with VTE vs. those without VTE	A D-dimer level cut-off value of 1.5 μg/mL could be used to predict VTE
Tang et al. 2020	COVID-19 survivors vs. nonsurvivors	About 28.36% and 85.7% of the COVID-19 patients with DIC exhibited fibrinogen level <1 g/L and D-dimer level >3 mg/dL, respectively
Qui et al. 2020	Mild COVID-19 vs. moderate COVID-19; all pediatric patients	Mild COVID-19 patients exhibited significantly lower levels of D-dimer compared to moderate COVID-19 patients
Liu et al. 2020	Mild COVID-19 vs. severe COVID-19	Mild COVID-19 patients exhibited significantly lower levels of D-dimer compared to severe COVID-19 patients
Zhang et al. 2020	Mild or moderate COVID-19 vs. severe COVID-19	Mild/moderate COVID-19 patients exhibited significantly lower levels of D-dimer compared to severe COVID-19 patients
Chen et al. 2020	Moderate COVID-19 vs. severe COVID-19	Moderate COVID-19 patients exhibited significantly lower levels of D-dimer compared to severe COVID-19 patients
Wu et al. 2020	COVID-19 patients with ARDS vs. those without ARDS	Risk of ARDS in COVID-19 patients directly correlated with the levels of D-dimer (p<0.001)
Zhou et al. 2020	Patients with no aggravated COVID-19 vs. Patients with aggravated COVID-19	The pathological progression of COVID-19 was not impacted by the levels of D-dimer
Wu et al. 2020	COVID-19 survivors vs. nonsurvivors	Higher levels of D-dimer significantly correlated with higher mortality risk among COVID-19 patients who presented with ARDS (p=0.002)

Tang et al. 2020	COVID-19 survivors vs. nonsurvivors	(i) Multivariate analysis revealed the level of D-dimer to be independently associated with 28-day mortality
(ii) Among the COVID-19 patients with levels of D-dimer >3.0 μg/mL, those who did not receive heparin exhibited a significantly higher 28-day mortality rate compared to those who received heparin (p=0.017)	Yin et al. 2020	Individuals suffering from both severe pneumonia and COVID-19 vs. individuals suffering from severe pneumonia but not COVID-19
Among the COVID-19 patients with levels of D-dimer >3.0 μg/mL, those who did not receive heparin exhibited a significantly higher mortality rate compared to those who received heparin (p=0.017)	Zhang et al. 2020	COVID-19 survivors vs. nonsurvivors

VTE, venous thromboembolism; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome.

4.2. Future Implications: Scope of Anticoagulation Therapy

Considering the COVID-19 pandemic, identifying therapies that improve outcomes is crucial. The findings presented in this review indicate that D-dimer could prove to be a potential biomarker to assess the disease severity level of COVID-19 patients and predict their outcome. This postulate is further supported by the analysis of Sakka et al., who suggested that levels of D-dimer could be helpful in categorizing the COVID-19 patients in terms of their disease severity levels at the time of admission to the hospital itself. They further reported that such categorization of the patients could facilitate personalized and more efficient clinical management in a timely manner based on their disease severity level [44]. Furthermore, several studies have shown that novel coronavirus infections lead to a significant increase in the formation of thrombi in the vascular system of COVID-19 patients. These findings indicate that apart from being a marker of elevated coagulation activity and prothrombosis in COVID-19 patients, D-dimer could also be involved in the pathogenesis of the disease [7]. Owing to the significant association of levels of D-dimer with prognosis and outcome of COVID-19 patients, the latest guidelines of the International Federation of Clinical Chemistry and Laboratory Medicine suggest that physicians must consider examination of levels of D-dimer in individuals suffering from COVID-19 [18, 45]. Recently, Long et al. also warranted the need to modify the thromboprophylaxis protocol for COVID-19 patients who are hospitalized [46]. In another study, Barnes et al. suggested that the modified prophylaxis protocol of COVID-19 patients must include anticoagulant therapies commencing immediately after admission to the hospital to reduce the rate of thrombi formation in such patients, provided such therapies do not lead to the risk of bleeding among the patients [47]. In this direction, Spyropoulos et al. further suggested that the application of any such modified prophylaxis protocol should be followed by an examination of a modified venous thromboembolism risk score to assess whether the patients are benefitting from the modified protocol [48].

Currently, the COVID-19 patients are managed using pharmacological DVT prophylaxis. However, this management approach is not specific to COVID-19 patients [49]. Acutely ill or hospitalized COVID-19 patients, including those receiving critical care, were found to have high rates of venous thromboembolism (VTE). In these patients, the best thromboprophylaxis strategy is still uncertain [50]. Recently, the American Society of Hematology (ASH) guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic intensity anticoagulation for patients with COVID-19–related acute illness who do not have suspected or confirmed VTE [51]. Conte G et al. thought that recommendations for using pharmacological DVT prophylaxis are mostly based on the results of

research with medical patients who did not have COVID-19. Furthermore, it is unclear whether antithrombotic prophylaxis in COVID-19 patients should be guided by risk assessment models (as was the traditional approach in nonsurgical hospitalized patients prior to the present epidemic), D-dimer values, or clinical judgment alone [52]. In a multicenter, randomized, controlled trial including patients hospitalized with confirmed COVID-19 and elevated D-dimer concentration, a 30-day course of therapeutic anticoagulation with rivaroxaban at 20 mg daily (and enoxaparin 1 mg/kg twice daily for clinically unstable patients) did not result in better clinical outcomes when compared with in-hospital prophylactic anticoagulation with heparin. Therapeutic anticoagulation for 30 days with rivaroxaban or enoxaparin led to a higher incidence of major or clinically relevant nonmajor bleeding than did inhospital prophylactic anticoagulation [53]. According to Al-Ani et al., the following anticoagulants hold great potential in reducing the frequency of microthrombi formation in COVID-19 patients [54].

(1) Heparin: In their recent retrospective review, Tang et al. assessed the effect of heparin therapy on the mortality rate of COVID-19 patients. They reported that, overall, there was no significant difference in the mortality rates of COVID-19 patients who either received or did not receive heparin. However, the COVID-19 patients with abnormally high levels of D-dimer who received heparin exhibited significantly lower mortality rates than the COVID-19 patients with abnormally high levels of D-dimer but who did not receive heparin. The former result could be attributed to the fact that other clinical settings and treatment modalities received by the patients were not revealed, impacting the mortality of the COVID-19 patients [55, 56].

(2) TPA: Although to date very few studies have assessed the effects of TPA administration on mortality rates of COVID-19 patients, their results have been positive. These studies have reported significant improvement in the ventilator parameters and oxygenation index of severely ill COVID-19 patients after TPA administration [55].

(3) Direct oral anticoagulants (DOACs): This category of anticoagulants seems to be effective in COVID-19 patients based on the findings of Testa et al. who reported a marked increment in the plasma levels of DOAC in COVID-19 patients who received antiviral medications [57].

A recent study published by Spyropoulos et al. reported that the use of therapeutic-dose low molecular weight heparin (LMWH) for thromboprophylaxis in high-risk inpatients with COVID-19 decreased thromboembolism and mortality in their trial. High-dose anticoagulant therapy altered the course of illness in patients who were not in the intensive care unit but had a very high risk of thromboembolism and mortality (36.1% incidence in the standard dose group) [58].

5. Conclusion

In conclusion, it is clearly evident that levels of D-dimer are directly associated with the disease severity among COVID-19 patients. Novel coronavirus infections promote inflammatory and coagulation reactions, leading to an increase in thrombotic event rates. Currently, the evaluation of levels of D-dimer has not been adopted in the routine laboratory assessment of COVID-19 patients. Laboratory testing for D-dimer and proinflammatory cytokines could help to categorize the COVID-19 patients based on the severity of their illness. This could, in turn, be helpful in adequate and more efficient management of such individuals. We also recommend that future investigators should focus on conducting more comprehensive and multicentric prospective studies to elucidate further the association of levels of D-dimer with the levels of proinflammatory cytokines and with the thrombotic pathways, especially in COVID-19 individuals. Finally, we propose that physicians should consider using anticoagulant therapies to counter the upregulated thrombotic activity in COVID-19 patients.

Authors' Contributions

All authors made substantial contributions to conception and design and/or writing. They participated in drafting the review and revising it critically for important intellectual content, and they gave final approval of the version to be submitted and any revised version.

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DETAIL

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Pediatric Sickle Cell Disease in Sudan: Complications and Management

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ABSTRAK (ENGLISH)

Background. Sickle cell disease (SCD) is a life-threatening genetic disorder due to the formation of sickle hemoglobin molecule (HbS) that polymerizes in hypoxic conditions leading to SCD-related complications. Different approaches have been used in the management of SCD including symptomatic management, supportive management, and preventive management. *Objectives*. To assess the management of SCD in pediatric patients in Gaafar Ibnauf Referral Hospital in Khartoum locality, Sudan. *Method*. A descriptive, retrospective, hospital-based study was conducted in Gaafar Ibnauf Hospital using a data collection sheet. The study included all medical files of pediatric patients with SCD attending the hospital during the period from the first of April 2018 to the first of July 2018. The data were analyzed using descriptive statistics and the chi-square test. $P<0.05$ was considered statistically significant. *Results*. Out of 207 pediatric patients, 53.1% were females (mean age of 7.5 ± 3.1 years), with a 1.1 : 1 female:male ratio and low socioeconomic status. Only 4.3% of participants had health insurance. The Messeryia tribe in western Sudan had the highest prevalence of the disease among the Sudanese tribes (11.1%). Vaso-occlusive crisis (33.3%), infections (13.5%), and neurological complications (10.6%) were the most frequent complications reported during routine visits. After initiation of management, only 3.4% of pediatric patients had hemolytic crises, and 1.4% of the anemic patients had splenomegaly. 100% of patients received folic acid, 73.9% used hydroxyurea, and 69.6% underwent blood transfusion for the management of SCD. Prophylactic penicillin was prescribed for 15% of patients, and 41.1% were immunized with pneumococcal vaccine (PPSV23). Most patients had been scheduled for planned follow-up visits every 3–6 months (93.2%). Hydroxyurea and blood transfusion

significantly reduced fever and vaso-occlusive crisis. *Conclusion*. The SCD treatment protocol in Gaafar Ibnauf Children's Hospital, involving preventive and symptomatic therapy, is consistent with the internationally implemented protocols for SCD management. However, immunization and prophylactic penicillin approaches are deficient.

TEKS LENGKAP

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1. Introduction

Sickle cell disease (SCD) is a life-threatening genetic disorder due to the formation of sickle hemoglobin molecule (HbS) with low affinity to oxygen. In the presence of hypoxia, HbS polymerizes and ultimately results in sickled red blood cells that rupture leading to hemolytic anemia. Moreover, the sickled cell also results in vascular occlusion causing tissue infarction, organ damage, and pain [1].

SCD affects many people throughout the globe, particularly those descending from Sub-Saharan Africa, the Middle East, and South Asia. In general, SCD exists in the malarial regions of tropical areas. However, migration from a malarial area increases the number of children with SCD in Europe and North America [2–4]. In the United States, SCD affects 1 in 500 African Americans. It is estimated that the population of sickle cell disease is approximately 4.4 million people, whereas 43 million are estimated to have sickle cell trait [5]. In Sudan, sickle cell disease is a major health problem in certain parts of the country, particularly the western region. The HbS allele frequently exists among the Misseriya tribe, and it is estimated to range from 18.2% in Kordofan to 30.4% in Darfur [6, 7].

The main complications of SCD include pain syndromes, hemolytic anemia, and organ damage/failure [8]. The incidence of complications varies with age from infancy through adult life. Recurrent pain episodes, the hallmark of the disease, result from acute painful vaso-occlusive crises (VOCs) when the sickled cells block the blood vessels. The pain is usually nociceptive in nature, which varies from patient to patient. It could be acute or chronic, somatic or visceral, unilateral or bilateral, localized or diffuse. Generally, pain affects long bones, joints, and the back; however, the scalp, face, jaw, abdomen, and pelvis may be involved [8]. In addition, bacterial infections and anemia are common complications in children with SCD [9,10]. Acute chest syndrome (ACS), splenic sequestration, and multiorgan damage are considered life-threatening conditions that require immediate hospitalization. Cardiopulmonary complications, including cardiomyopathy, pulmonary hypertension, and sudden cardiac death, are the most common causes of morbidity and mortality. Children with SCD are at high risk for developing thrombosis and stroke. SCD is now recognized as a systemic disease, which causes widespread tissue/organ injury, including inflammatory dysfunction and coagulation abnormalities. All children with SCD should be screened annually with transcranial Doppler ultrasonography (TCD). It is highly recommended for children with SCD from 2–16 years of age [8, 11–13].

The management of SCD and its complications requires major approaches, including supportive management, symptomatic treatment, as well as preventative measures. The ultimate goal of treatment is to alleviate the symptoms and to maintain a good quality of life [8, 14].

A published guideline [15] strongly recommends daily oral prophylactic penicillin for children with SCD up to the age of 5 years to reduce the risk of infections. In addition, immunization especially pneumococcal vaccination, was strongly recommended by SCD treatment guidelines [15,16]. The American Society of Hematology (ASH) guideline recommends opioids for the treatment of acute pain associated with vaso-occlusive crisis. For adults who have SCD-related chronic pain, the ASH guideline suggests the use of nonopioid analgesics such as NSAIDs, duloxetine, gabapentinoids, or tricyclic antidepressants, as options for pain management [16]. Blood transfusion reduces the level of HbS, thereby it is used to treat acute symptomatic anemia as well as treating and preventing many SCD complications [15]. To reduce the risk of stroke, especially in children with abnormal transcranial Doppler velocity, regular blood transfusion for at least one year is recommended to reduce HbS levels below 30% and to maintain Hb levels >9.0 g/dL. Assessment of iron overload is required to initiate iron chelators when indicated. Moreover, the ASH guideline suggests hydroxyurea therapy for children (ages 2–16 years) who live in low-middle-income areas

(where regular blood transfusions and chelation therapies are not available or affordable). Hydroxyurea therapy decreases SCD-related complications (such as VOCs, ACS, hospitalization, and mortality rate) by increasing fetal hemoglobin (HbF) [15, 17].

SCD is a life-threatening disorder that is associated with acute and chronic complications interfering with daily activities and the quality of life of patients. In Sudan, SCD mainly affects children who continue to suffer from repetitive pain crises and frequent severe complications, and ultimately leads to early death. Therefore, specialized medical care focusing on prevention and regular assessment of disease management is urgently needed to reduce morbid events as well as the mortality rate. This study aimed to assess the management of sickle cell disease in pediatric patients at Gaafar Ibnauf specialized pediatric hospital in Sudan in light of international guidelines.

2. Methodology

2.1. Study Design and Setting

A descriptive, retrospective, hospital-based study was carried out in Gaafar Ibnauf Pediatric Hospital, Khartoum state, Sudan. Gaafar Ibnauf Hospital is the biggest referral specialized pediatric hospital in Sudan, receiving patients from all over the country. It encompasses nine units of different specialties in pediatrics (cardiology, neurology, gastroenterology, respiratory, hematology, and nursery).

2.2. Study Population

Study populations consisted of pediatric patients with SCD attending Gaafar Ibnauf Hospital and outpatient's clinic. All patients' files during the period (1 April 2018–1 July 2018) were manually screened.

2.2.1. Inclusion Criteria

Medical files of pediatric patients with SCD attending Gaafar Ibnauf Hospital from April to July 2018 were included in this study.

2.2.2. Exclusion Criteria

Incomplete patients records were excluded from the study.

2.3. Sampling Technique and Sample Size

A total coverage sampling technique was used in the current study. Two hundred and seven medical files of pediatric patients with SCD were selected based on the inclusion and exclusion criteria.

2.4. Data Collection Tool

The data were collected using a data collection sheet constructed by the researchers based on the study objectives. The data collection sheet consists of three parts. The first part covered the patients demographic data. The second part listed the common complications of SCD, and the third part covered diagnostic tests, management of the disease, and therapeutic monitoring throughout the scheduled follow-up visits.

2.5. Statistical Analysis

The data was analyzed using Statistical Package for Social Science Software (SPSS, version 20) and Microsoft Excel. For numerical data, the mean and standard deviation were calculated. For categorical data, descriptive statistics such as frequency and percentage were used to summarize the results. The Chi-square test was used to describe the association between variables. Pvalue <0.05 was considered statistically significant.

2.6. Ethical Considerations

The ethical approval was obtained from the Research Board at the University of Khartoum, Faculty of Pharmacy (Research Ethics Committee, No. 59-5-3–2018). In addition, ethical clearance has been obtained from the Research Department, the Ministry of Health, Sudan. Permission to perform the study was obtained from the general director of the hospital. To ensure confidentiality of the patients' information, coded data collection sheets were used.

3. Results

3.1. Sociodemographic Characteristics of Patients

The study included 207 patients, with a mean age of 7.5 ± 3.1 years. More than half of patients (53.1%) were females, with a 1.1 : 1 female:male ratio and low socioeconomic status (53.6%). Only 4.3% had health insurance. Two-thirds of patients (66.2%) had no family history of sickle cell disease (Table 1).

Table 1

Patient's socio-demographic characteristics (*N*=207).

Demographic Data	Mean	Std. deviation (%)
Age	7.5	3.1
Gender	Frequency	Percent
Male	97	46.9
Female	110	53.1
Socioeconomic status		
Low	111	53.6
Moderate	80	38.6
Unknown	16	7.7
Health insurance		
Yes	9	4.3
No	198	95.7
Family history of sickle cell disease		
Yes	64	30.9
No	137	66.2
Unknown	6	2.9

3.2. Distribution of Sickle Cell Disease among Different Tribes in Sudan

Messeryia (11.1%) and Selehab (8.2%) tribes had the highest rate of SCD among the Sudanese tribes (Table 2).

Table 2

Rate of sickle cell disease in the Sudanese tribes.

Sudanese tribes	Frequency	Percent
Messeryia	23	11.1
Selehab	17	8.2

Barno	14	6.8
Fallata	13	6.2
Bargo	13	6.2
Four	7	3.4
Rezegat	6	2.9
Rashyda	6	2.9
Hosa	6	2.9
Noba	5	2.4
Jammoeia	5	2.4
Zagawa	4	1.9
Benihalba	4	1.9
Bedireia	4	1.9
Taayisha	3	1.4
Omtenger	3	1.4
Rofaien	2	1
Masalti	2	1
Kanania	2	1
Hawazma	2	1
Gazami	2	1
Deedab	2	1
Dago	2	1
Berti	2	1
Baggara	2	1

Gaaline	2	1
Nemawia	1	0.5
Edasha	1	0.5
Danjo	1	0.5
Notrecorded	51	24.6

3.3. Diagnostic Laboratory Tests for Sickle Cell Disease and Routine Laboratory Monitoring for Patients with Sickle Cell Disease

The major laboratory test that had been carried out for SCD diagnosis in the participants was hemoglobin electrophoresis (96.1%). All patients had been routinely monitored for hematological problems using a complete blood count test. 37.7% and 7.7% of patients had been monitored for liver and renal function, respectively. Transcranial Doppler ultrasonography (TCD) or pulmonary function tests were not routinely requested for the patients at each follow-up visit (Table 3).

Table 3

Diagnostic laboratory tests and routine laboratory monitoring for patients with sickle cell disease.

Test	Frequency	Percent
Diagnostic laboratory tests		
Sickling test	4	1.9
Solubility test	3	1.5
Haemoglobin electrophoresis	199	96.1
HPLC	0	0.0
Isoelectric focusing test	0	0.0
Not reported	1	0.5
Routine laboratory tests		
CBC with Reticulocyte Count	207	100.0
Liver Function Test (LFT)	78	37.7
Renal Function Test (RFT)	16	7.7
EKG and Echocardiogram	7	3.4

Abdominal Ultrasound	4	1.9
Ophthalmology Test	2	1.0
Pulmonary Function Test	0	0.0
Transcranial Doppler Ultrasonography	0	0.0

3.4. Complications of Sickle Cell Disease among Participants

One-third of patients (33.3%) experienced vaso-occlusive crisis/pain, including 1% of patients having acute chest syndrome (ACS). 13.5% of patients had developed infections, with 9.6% infected with pneumococcal and meningococcal bacteria (respiratory tract infections, meningitis, and sepsis), whereas 3.9% had malaria infection. 4.3% of patients had experienced GIT symptoms. 11.1% and 10.6% of patients had experienced fever and neurological complications (such as hemorrhagic or ischemic stroke and headache). Anemia (hemolytic crises) had been encountered in 3.4% of patients, and 1.4% of the anemic patients had splenomegaly. Hepatomegaly/jaundice has been observed in 3.4% of patients (Figure 1).

[figure omitted; refer to PDF]

3.5. Scheduled Follow-Up Visits in Patients with SCD

The majority of patients (93.2%) had been scheduled for follow-up visits every 3–6 months (Figure 2).

[figure omitted; refer to PDF]

3.6. Management of Patients with Sickle Cell Disease

This study showed that folic acid had been prescribed for all patients (100%), and 73.9% of patients had been treated with hydroxyurea therapy. The starting dose of hydroxyurea was 10 mg/kg/day and then the dose was escalated to 15 m/kg/day up to 35 mg/kg/day. The majority of patients received 15 mg/kg/day. Only 15% of patients received prophylactic penicillin with the majority of them (87.1%) receiving amoxicillin. More than half of patients (58.9%) were unvaccinated, and 41.1% of patients had been immunized with pneumococcal vaccine. All children younger than 2 years received 3 doses of the 13-valent pneumococcal conjugate vaccine (PCV13). Children 2–5 years old were administered 1–2 doses of PCV13 if they were unvaccinated or had received incomplete doses of PCV13. After completion of the PCV13 vaccine series, children aged ≥2 years received 1 dose of the 23-valent pneumococcal polysaccharide vaccine (PPSV23), with a booster dose 5 years later. More than two-thirds of patients (69.6%) were subjected to blood transfusions, with 13.9% ($n=20$) of them undergoing chronic blood transfusions monthly for 3 years (Table 4).

Table 4

Management of patients with sickle cell disease ($N=207$).

Management	Frequency	Percent
Folic acid	207	100.0
Hydroxyurea	153	73.9
Supplements	95	45.9
Antibiotics for infections	15	7.2

Analgesics	10	4.8
Prophylactic penicillins (*N*=31)	31	15.0
Amoxicillin	27	87.1
Penicillin VK	4	12.9
None	176	85.0
Vaccination		
Pneumococcal vaccine	85	41.1
None	122	58.9
Blood transfusion		
Yes	144	69.6
No	63	30.4

3.7. Association between SCD Complications and Treatment Modalities

The use of hydroxyurea for the management of SCD was significantly associated with a low risk of fever (*P=0.045*). A significant reduction of vaso-occlusive crisis/pain (P=0.04) has been observed after blood transfusion (Table 5).

Table 5

Association between complications of SCD and the treatment modalities.

Complications	Hydroxyurea (*N*=153)		P*value*
Yes	No	Fever	13 (8.5%)
140 (91.5%)	0.045*	Vas-occlusive crisis	54 (35.3%)
99 (64.7%)	0.30	Blood transfusion (*N*=145)	
Vas-occlusive crisis	42 (29%)	103 (71%)	0.04*

*P≤0.05

4. Discussion

Sickle cell disease (SCD) is an inherited blood disorder associated with acute and chronic complications and early death [18]. In Africa, thousands of children are born with SCD, and 90% of them die before the age of 5 years [3]. To date, there are no established programs in Africa for screening and clinical interventions for SCD management. Screening, pneumococcal prophylaxis, affordable treatment options, and caregivers' education effectively reduce child mortality due to SCD [19]. Providing optimal and comprehensive care to individuals with SCD can be

challenging. Thus, implementing guidelines that provide evidence-based recommendations for the management of this life-threatening condition is of crucial importance and helps healthcare professionals to improve their practice [15]. This study aimed to assess the management protocol used for SCD in Gaafar Ibnauf Hospital in Sudan.

In this study, the participants were young children with a mean age of 7.5 ± 3.1 years. Most patients were females with low socioeconomic status. The results showed that 11.1% of the cases were from the Messeryia tribe in western Sudan. As reported in the literature, the prevalence of SCD in Sudan ranges from 2 to 30.4%, with a higher prevalence among tribes in western Sudan [6, 7, 20]. This could be due to migration from West African countries where the high prevalence of the disease is well documented [21].

In routine laboratory monitoring, all patients have been routinely monitored for complete blood counts, and unfortunately, transcranial Doppler ultrasonography (TCD) is not a routine practice at each follow-up visit. According to published guidelines, annual screening of stroke using transcranial Doppler ultrasonography is recommended for all children with sickle cell disease [15]. However, in Gaafar Ibnauf Hospital, TCD is only requested when neurological symptoms appear, and this practice could be due to the low socioeconomic status of the patients, unavailability, and unaffordability of the test.

Vaso-occlusive crises (VOCs), infections, fever, and neurological complications are the most serious complications that are reported during routine visits. Pneumococcal and meningococcal infections are the most commonly encountered complications in pediatric SCD. Hemorrhagic or ischemic stroke and headache are the most frequently encountered neurological complications in the current study. This finding is consistent with a previous study in Africa which demonstrated stroke as a common neurological complication of SCD [22]. In Africa, some complications such as silent brain infarcts, peripheral neuropathies, neurocognitive deficits, encephalopathy, or moyamoya disease are often underestimated because of the unavailability and unaffordability of diagnostic tests such as neuroimaging, transcranial Doppler ultrasonography, electroencephalogram (EEG), and neuropsychological evaluation [22]. Acute chest syndrome is a life-threatening complication, but it is not common in this study.

Anemia (hemolytic crises; Hb Plasmodium species and is frequently reported in children with SCD (HbSS) in malaria-endemic countries [23]. These contradictory results seemed to be attributed to the early development of autosplenectomy in most children attending the hospital. Repeated attacks of VOCs cause autosplenectomy, rendering our patients more vulnerable to systemic infections. Autosplenectomy occurs because caregivers do not seek medical help at the earliest sign of the disease and most children start medications, especially hydroxyurea, at a later age (more than 9 months) after the onset of complications. This practice among patients could be related to a lack of good health education, low socioeconomic status, and health insurance coverage [24]. Moreover, most patients are from rural areas in western Sudan where there is a lack of health facilities. The low rate of malaria infection could be attributed to less exposure of patients to malaria infection by using preventive and control measures of malaria such as mosquito nets and repellents. Moreover, inaccessibility of screening tests and underreporting of complications may lead to underestimation of patients with splenomegaly and malaria.

In this study, most patients were unvaccinated and did not receive prophylactic penicillin. The high incidence of infections observed among participants in the current study may be explained by the failure in implementing an effective immunization protocol and the physician's nonadherence to guidelines, regarding antibiotic prophylaxis for children with SCD. Initiation of penicillin prophylaxis up to the age of 5 years, in addition to vaccination, is recommended to reduce the risk of developing serious bacterial infections [14, 15, 25]. Low prescription rates of prophylactic penicillin may be attributed to fear from the emergence of penicillin resistance, noncompliance of physicians to treatment guidelines, and nonadherence to medications in SCD patients [15, 26, 27]. Oral amoxicillin was the most frequently used prophylactic penicillin among the participants. Children with SCD in this study received only pneumococcal vaccine which was given according to clinical practice guidelines of pneumococcal immunization. Children younger than 2 years should receive 4 doses of the 13-valent pneumococcal conjugate vaccine (PCV13). Before starting the 23-valent pneumococcal polysaccharide vaccine (PPSV23), children 2–5 years old (unvaccinated or having received incomplete doses of PCV13) should be vaccinated with 1–2 doses of PCV13. After completion of the PCV13 vaccine series, children aged 2–18 years should receive 1 dose of PPSV23, with a

booster dose 5 years later [28]. As indicated in SCD treatment protocols, immunizations should include all children's routine vaccines with the addition of the flu vaccine, pneumococcal vaccine, and meningococcal vaccine [14].

In this study, hydroxyurea was prescribed to most participants, reflecting the physician's adherence to SCD treatment guidelines regarding this medication. The starting dose of hydroxyurea was 10 mg/kg/day and escalated to a maximum tolerated dose (maximum dose is 35 mg/kg/day). The majority of patients received hydroxyurea at a dose of 15 mg/kg/day. Although oral L-glutamine was approved by the FDA in 2017 to reduce the acute complications of SCD in adult and pediatric patients older than 5 years [14,29], it has not yet been used or even registered in Sudan.

In this study, more than two-thirds of patients received blood transfusions, with 13.9% of them undergoing chronic blood transfusions every month for 3 years to prevent primary or secondary stroke. Chronic transfusion is used when unremitting reduction of HbS (less than 30%) is required for stroke prevention [15]. The majority of the patients in this study received episodic transfusions (periodic transfusions) for acute chest syndrome, acute anemia, hepatic sequestration, progressive intrahepatic cholestasis, priapism, and sepsis. Simple blood transfusion was frequently used in comparison with exchange blood transfusion.

In this study, few patients received analgesics for the management of painful crises. The SCD treatment guidelines strongly recommend immediate initiation of nonopioid and opioid analgesics for the management of pain associated with VOC, based on the level of patient-reported pain [15]. It appeared that most patients had mild pain, and the main barrier of the frequent prescription of NSADs is the side effects of these medications.

The scheduled follow-up visits are necessary for effective disease control. In this study, most patients had been scheduled for planned follow-up visits every 3–6 months. It has been observed from the medical history of patients that VOC episodes and hospitalizations usually occur before the three-month check-up period. Therefore, a three-month check-up period is rather long for monitoring the therapeutic outcomes of children with SCD. As an observation, some patients are unable to adhere to their follow-up visit, and this could be due to a lack of awareness of patients or their caregivers about the benefit of follow-up visits. In addition, financial issues may be a reason for nonadherence to follow-up visits since most patients are of low socioeconomic status and without health insurance.

This study revealed that hydroxyurea and blood transfusion for the management of SCD significantly reduced fever (*P: 0.0*4) and VOCs (*P: 0.04*), respectively. However, patients taking hydroxyurea appeared to be healthier with less frequent VOCs and other complications than those not taking hydroxyurea. As reported in the literature, both hydroxyurea and blood transfusion are used to reduce SCD-related complications such as recurrent vaso-occlusive crisis and fever [29]. Insignificant effects of hydroxyurea in reducing VOCs could be attributed to the use of relatively low doses of hydroxyurea (15 m/kg/day) in most patients or patients' nonadherence to hydroxyurea therapy. Hydroxyurea requires a monitoring protocol to ensure the highest benefits and safety of the therapy. Low doses of hydroxyurea have minimal effect in fetal hemoglobin production that mitigates tendencies for red blood cell sickling and VOC [15, 29]. A previous study demonstrated that hydroxyurea at a dose of approximately 30 mg/kg/day significantly reduces sickle cell-related adverse events (such as VOC) when compared to hydroxyurea at a dose of 20 mg/kg/day [30].

5. Limitations

The study is a single-center study with a relatively small sample size that may affect the generalizability of the results. In addition, some medical files had been excluded because of poor documentation.

6. Conclusion

The prevalence of SCD in Sudan is higher in the Messeryia tribe, originating from western Sudan. The treatment protocol at Gaafar Ibnauf Hospital-Sudan includes hydroxyurea, analgesics, folic acid, and blood transfusions. This treatment protocol, involving preventive and symptomatic therapy, is consistent with the international implemented protocols for the management of SCD in children. However, immunization and prophylactic penicillin approaches are deficient. The use of hydroxyurea and blood transfusion for children with SCD significantly reduces fever and vaso-occlusive crisis, respectively. Unfortunately, recently approved drugs, such as L-glutamine, have not yet been used in hospitals.

7. Recommendations

(i) Ongoing communication between healthcare providers and patients or caregivers on the use of hydroxyurea will enable informed joint decision-making and empower patients to initiate hydroxyurea therapy.

(ii) Institution of comprehensive SCD centers focusing on life-long SCD management. Physicians, clinical pharmacists, and other healthcare workers involved in the care of SCD patients should be well trained and acquainted with current knowledge and standard practices in the treatment of SCD to improve treatment outcomes.

(iii) Patients should be counseled on the need for adherence to scheduled vaccinations and ensure that all patients have received all vaccines that have been recommended by SCD treatment protocols.

(iv) Communicate with health policymakers to provide free of charge medicines (hydroxyurea, folic acid, penicillin, and pneumococcal vaccine-23) and offer low-cost and high-quality laboratory tests for patients with SCD to increase the adherence to SCD treatment protocol.

(v) Intensify educational programs to enhance awareness of children and caregivers about the nature of the disease, possible complications that require immediate medical attention, the importance of antibiotic prophylaxis and vaccination to prevent life-threatening pneumococcal infections.

Authors' Contributions

Meysaa, G.T. participated in the conception, literature review, collection, and analysis of the data. Abdoon, I. contributed to the conception, study design, follow-up, interpretation of data, writing of the original manuscript, and providing critical revision of the manuscript. Osman, B. participated in reviewing, editing, and providing final approval of the manuscript. Abdalla, S.A. contributed to the drafting and proofreading of the manuscript. Mirghani H. M. contributed to reviewing, proofreading, and final approval of the manuscript. The manuscript has been read and approved by all authors.

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DETAIL

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Neonatal Screening for Sickle Cell Disease in Congo

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ABSTRAK (ENGLISH)

Introduction. Sickle cell disease is an autosomal recessive inherited disorder due to the mutation of a gene coding for the globin beta chain. The aim of this study is to update the epidemiological data on hemoglobinoses, in particular sickle cell disease in newborns in Congo. *Materials and Methods*. This was a descriptive cross-sectional study, conducted from October 1, 2019, to March 31, 2020, throughout the Congolese national territory. It involved

all full-term newborns, without distinction of nationality, aged 5 days or less, and whose parents consented to participate in the study. The blood samples, taken at the heel and collected on Whatman blotting paper, were analyzed using the HPLC Variant NBS machine. *Results*. In 2897 newborns (NN) screened, hemoglobin abnormalities were found in 603 NN (20.81%). The mean age of these newborns was 1 day (extremes 0 and 5 days). The male-to-female ratio was 1.03. Abnormal hemoglobins were mainly Hb S (*n*=597 (97.71%)); Hb C (*n*=5 (0.82%)); and variants (*n*=7 (1.15%)). The national prevalence of major sickle cell (MSC) syndromes and sickle cell trait was 1.35% and 19.43%, respectively. The prevalence ranged from 1.77% to 2.56% for MSS in four departments and from 20.5% to 25.8% for the sickle cell trait in six other departments. *Conclusion*. Data on homozygous sickle cell disease remain consistent with previous studies. However, further studies should clarify the molecular anomalies of the variants observed in our samples.

TEKS LENGKAP

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1. Introduction

Sickle cell disease is an autosomal recessive inherited disorder linked to the mutation of a gene coding for the beta chain of globin [1–3].

It is the first genetic disease in the world which mainly comprises four (4) primitive foci: African focus, Asian Peninsula, South-East Asia, and an incidental focus in the Balkans.

A distinction is made between heterozygous forms (AS) and homozygous forms (SS) which are part of the major sickle cell syndromes (MSS). The major sickle cell syndromes include the following entities: homozygous abnormal hemoglobin S, hemoglobin S associated with other abnormalities (C, D, and O), and intermediate forms of thalassemia. Multiple studies have been carried out worldwide on the prevalence of this genetic disorder [4–9]. In Africa, studies report a prevalence of 0.8 to 3% of major forms and 7 to 24% of heterozygous forms [4, 5, 10–16]. Studies in Congo have involved local sampling and analysis, most often carried out outside Congo [4, 16]. These analyses placed the frequency of sickle cell trait in Congo between 19 and 24% and the homozygous form around 1% according to neonatal samples [4, 16].

This study, which focuses on neonatal sampling, was conducted entirely in Congo. The samples were taken from newborns in all departments of the Republic of Congo, and the analyses were carried out on site. In order to update the data on sickle cell disease in Congo, we conducted this study to determine the prevalence of sickle cell disease and to estimate the variants of hemoglobin (Hb) in newborns in each department of Congo.

2. Materials and Methods

This was a cross-sectional descriptive study conducted from 1 October 2019 to 31 March 2020 over the entire national territory of Congo (Figure 1). The Republic of Congo is located in sub-Saharan Africa, in the sickler belt. It is made up of 12 departments (Figure 1) in which samples were collected and sent to the Centre National de Reference de la drepanocytose (CNRDr) for analysis. The CNRDr is a subregional facility, open to the public in 2016, specialised in the management of genetic diseases including sickle cell disease. It comprises care, imaging, and medical biology units.

[figure omitted; refer to PDF]

The target population consists of full-term newborn babies (NBs) born in the Congolese territory. All NBs without distinction of nationality, aged 5 days or less, were included in the study. We did not include all NBs in the posttransfusion period and those in intensive care. Furthermore, only the NBs whose parents had given their informed consent were included. Only those whose parents gave consent were screened. Refusal to screen a newborn was a criterion of exclusion. The recruitment was carried out in a comprehensive way.

Considering the prevalence of the sickle cell trait of 21% [17] and the effect of the sampling design set at 1.5 and the imponderables estimated at 5%, the minimum sample size required for this study is 406. The number 406 corresponds to the minimum of patients needed to carry-on the study. It is not the sample of our study but the

minimum required. The minimum sample size for each department (cluster) was calculated by weighting the national minimum baseline sample size (406 NBs) according to the size of the population in the department. By rounding up these numbers, the minimum sample size selected was 412, broken down by department (Table 1)

Table 1

Minimum sample size by department.

Department	Population census of 2007	Minimum newborn size to be tested	Number of newborns tested
Brazzaville	1733271	151	1560
Pointe Noire	902828	79	370
Bouenza	390032	34	113
Pool	298580	26	132
Niari	291865	26	179
Plateaux	220328	20	121
Cuvette	196930	18	124
Likouala	194507	17	60
Lekoumou	121639	11	54
Kouilou	116065	11	38
Sangha	108211	10	68
Cuvette-Ouest	92123	9	78
Total	4666379	412	2897

For each newborn baby, a drop of blood was collected at the heel on Whatman 903TM (903 protein saver card) blotting paper under aseptic conditions. The samples were stored for a maximum of 72 hours in pouches (Multi-Barrier Pouches) with desiccant from GE Healthcare company laboratories. They were analyzed using the cation exchange high-performance liquid chromatography (HPLC) procedure (BioRad Variant NBS). Patient profiles were obtained by ranking hemoglobins in descending order of magnitude (thus, an FSA profile assumes a hemoglobin F concentration greater than hemoglobin S concentration and the latter greater than hemoglobin A concentration). The chromatographic profile of MSS was established in the presence of Hb: FS, FSC, FSE, FSD, FSA, FSE, and FSa. The data obtained were entered and processed using Microsoft Excel version 17.2 and R 3.6.3 software [18]. Qualitative variables were presented as numbers and percentages. Ethical clearance was obtained from the Comité Ethique de Recherche en Science de la Santé (CERSSA).

3. Results

At the end of this study, we obtained a total of 2,897 newborns, 603 of whom had abnormal hemoglobins, being

20.81%. The mean age of these newborns was one (01) day with extremes ranging from 0 to 5 days and a sex ratio (F/M) of 1.03. They were born at 38 (q1 36–q3 39) weeks of amenorrhea with an average weight of 3114 ± 567 g. Figure 1 illustrates the prevalence of abnormal hemoglobin in newborns by department.

The abnormal hemoglobins found were Hb S (*n* = 597; 97.71%), Hb C (*n* = 5; 0.82%), Hb D (*n* = 1; 0.16%), Hb E (*n* = 1; 0.16%), Hb Bart (*n* = 1; 0.16%), and unidentified Hb (*n* = 7; 1.15%). The distribution of the different types of abnormal hemoglobin by department is described in Table 2.

Table 2

Distribution of abnormal hemoglobins (Hb) in NBs by department between November 2019 and March 2020.

Department	HbS, *n* (%)	Autre Hb*, *n* (%)	HbC, *n* (%)	HbE, *n* (%)	HbBart, *n* (%)	HbD, *n* (%)
Bouendza	15 (2.5)	2 (28.6)	—	—	—	1 (100)
Brazzaville	314 (52.6)	1 (14.3)	5 (100)	—	1 (100)	—
Cuvette Centrale	32 (5.4)	1 (14.3)	—	—	—	—
Cuvette-Ouest	18 (3.0)	—	—	—	—	—
Kouilou	4 (0.7)	—	—	—	—	—
Lekoumou	12 (2.0)	—	—	—	—	—
Likouala	6 (1.0)	—	—	—	—	—
Niari	46 (7.7)	2 (28.6)	—	—	—	—
Plateau	23 (3.9)	—	—	—	—	—
Pointe Noire	90 (15.1)	—	—	1 (100)	—	—
Pool	31 (5.2)	1 (14.3)	—	—	—	—
Sangha	6 (1.0)	—	—	—	—	—
Total	597 (100)	7(100)	5 (100)	1 (100)	1 (100)	1 (100)

n : number; *: unidentified Hb variant.

Among the 2,897 newborns registered, major sickle cell syndrome (MSS) was found in 39 NBs and the sickle cell trait was found in 563, representing national prevalences of 1.35% and 19.43%, respectively (Table 3).

Table 3

Prevalence of sickle cell disease among newborns according to the departments of Congo between November 2019 and March 2020.

Department	Total, *n* (%)	Carrier Hb AA, *n* (%)	Carrier Hb AS/AC, *n* (%)	MSS*, *n* (%)

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Bouendza	113 (3.90)	98 (86.7)	13 (11.5)	2 (1.77)
Brazzaville	1560 (53.8)	1241 (79.6)	298 (19.1)	21 (1.35)
Cuvette Centrale	124 (4.28)	92 (74.2)	32 (25.8)	—
Cuvette-Ouest	78 (2.69)	60 (76.9)	16 (20.5)	2 (2.56)
Kouilou	38 (1.31)	34 (89.5)	4 (10.5)	—
Lekoumou	54 (1.86)	42 (77.8)	12 (22.2)	—
Likouala	60 (2.07)	54 (90.0)	6 (10.0)	—
Niari	179 (6.18)	133 (74.3)	44 (24.6)	2 (1.12)
Plateau	121 (4.18)	98 (81.0)	22 (18.2)	1 (0.83)
Pointe Noire	370 (12.8)	280 (75.7)	81 (21.9)	9 (2.43)
Pool	132 (4.56)	101 (76.5)	29 (22.0)	2 (1.52)
Sangha	68 (2.35)	62 (91.2)	6 (8.82)	—
Total	2897 (100)	2295 (79.21)	563 (19.43)	39 (1.35)

⁎MSS: major sickle cell syndrome (FS, FSE, and FSA).

Heterozygous qualitative hemoglobin abnormalities were AS (n=551 (97.87%)) and AC (n=5 (0.89%)).

Table 4 reports the prevalence of the sickle cell trait and MSS phenotypes according to the departments of Congo.

Table 4

Distribution of abnormal Hb chromatographic profiles in newborns according to departments between November 2019 and March 2020.

Department FAS⁎	Heterozygous profile		MSS profile		
	FAC, n (%)	FS, n (%)	FSA⁎⁎, n (%)	FSE, n (%)	Bouendza
13 (100)	—	1 (50)	1 (50)	—	Brazzaville
293 (98.32)	5 (1.68)	8 (38.1)	13 (61.9)	—	Cuvette Centrale
32 (100)	—	—	—	—	Cuvette-Ouest

16 (100)	—	—	2 (100)	—	Kouilou
4 (100)	—	—	—	—	Lekoumou
12 (100)	—	—	—	—	Likouala
6 (100)	—	—	—	—	Niari
44 (100)	—	1 (50)	1 (50)	—	Plateau
22 (100)	—	—	1 (100)	—	Pointe Noire
81 (100)	—	4 (44.44)	4 (44.44)	1 (11.11)	Pool
29 (100)	—	—	2 (100)	—	Sangha
6 (100)	—	—	—	—	Total

⁎6 cases of unidentified Hb variant and 1 Hb FASD; ⁎⁎FSA and FSa profile.

4. Discussion

This study's objective was to update the epidemiological data on sickle cell disease in Congo. The systematic screening approach was favored over the approach targeting NBs from parents with a family history of sickle cell disease, firstly, because healthy AS carriers do not express the disease and are often unaware of their status, which makes it difficult to identify subjects at risk and, secondly, because of the high prevalence of the S gene in the Congo Basin. This screening was carried out using the HPLC variant NBS technique, which has the advantage of being fully automated but also has a high sensitivity to detect normal neonatal hemoglobins (Hb F and Hb A) and the main hemoglobin variants (Hb S, C, E, and D).

In our study, the sex ratio (1.03), in favour of men, was similar to that reported in the literature [5, 13, 14, 19–21]. The average weight of newborns with abnormal hemoglobins was comparable to observations made by Munyanganizi in Rwanda and Kafando in Burkina Faso [10, 19]. It was lower than the one reported by McGann in Angola, which found an average weight of 3.201 ± 526 g [15]. Dietary, environmental, and genetic factors could explain these differences.

The prevalence of abnormal hemoglobin was 20.8%, mainly represented by hemoglobin S (97.71%). The geographical location of the Republic of Congo in the sickler belt and the endemic nature of malaria in Congo could be one of the factors favoring this condition. Indeed, in order to better resist malaria, the populations of this region have undergone mutations that have led to the appearance of hemoglobin S. Subjects carrying this mutation in its heterozygous form present a certain resistance to *Plasmodium falciparum* 22. A selective pressure with the evolution of the disease would have contributed to the increase in its prevalence. Results found in the literature indicate abnormal hemoglobin frequencies ranging from 0.22% to 31% [4, 5, 9, 13, 20, 23–25]. Some of these observations are comparable to ours [4, 5]; on the other hand, others had different results from ours [9, 13, 20, 23–25]. Results comparable to ours can be justified by the fact that these studies were carried out in Central Africa in the Congo Basin, the epicenter of sickle cell disease as in our case [4, 5, 22]. The results differing from ours can be explained by the fact that these screenings were carried out in nonendemic or low-malaria-endemic areas where sickle cell disease cases are mainly imported cases or from families with relatives from highly endemic areas. This justifies the need for the establishment of a national program of systematic screening for sickle cell anemia in order to provide early management of newborns living with sickle cell anemia. Moreover, early management makes it possible not only to delay the onset of complications but also to undertake genetic counseling of the parents of

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newborn babies living with sickle cell anemia [25–27].

Sickle cell trait prevalences of around 25% were obtained in some departments (Cuvette Centrale, Niari, and Pointe Noire) and 10% in others (Sangha, Likouala, Kouilou, and Bouendza). The low prevalence in these regions can be justified not only by their relatively small numbers compared to those of other departments but also by cultural habits regarding marriage.

The main abnormal Hb encountered was Hb S (97.71%) and C (0.82%). Variant C was found only in NBs with Malian parentage. This observation is similar to that made by some authors [6, 13, 14, 20, 24, 28], but differs from others in West Africa where Hb C predominates in most series 10. Indeed, Hb C is the most common abnormal Hb in West Africa and more particularly in Burkina Faso where it originated [29].

The prevalence of MSS found in our study was higher than that of our Congolese predecessors (1.35% versus 1%). The increase in prevalence is explained by the fact that 2010 study [4] was conducted in only two cities, whereas this study covered the entire country. Furthermore, the MSS profiles observed in our study were FS, FSE, and FSA, whereas they reported only one hemoglobin profile (FS). The type of equipment used in 2010 and the criteria used to define MSS could justify these differences.

In addition, MSS prevalences ranging from 0.06% to 3% have been reported in Europe, South America, Central Africa, and other countries. These variations could be justified not only by the fact that MSS is endemic in some regions while in others, it is mainly imported cases but also by the lack of knowledge of sickle cell disease in regions of high prevalence and the existence of consanguineous marriages [5–7, 9, 11, 12, 14, 15, 21, 23, 24, 28].

Similarly, the prevalence of MSS is heterogeneous within the departments of Congo. It predominates in some departments where its prevalence is higher than that observed at the national level (Table 3). Cultural habits in terms of choice of spouse, the lack of systematization of premarital screening, the mere availability of the Emmel test, and the lack of awareness in some departments could explain this disparity and, hence, the interest in setting up a capacity-building system for awareness raising, screening of couples at risk, and even genetic counseling in order to help reduce the prevalence of sickle cell disease. In addition, it will make it possible to initiate prophylaxis with penicillin therapy, which substantially reduces the morbidity and mortality of NBs [27, 30].

With regard to the sickle cell trait, as in the study by Mpemba et al., its national prevalence is 19.43%. It varies from one department to another (Table 3). In addition, we observed that the department of Cuvette Centrale, although it has a high prevalence of sickle cell trait, has fewer cases of MSS (Table 3). These facts could be justified by the health education of the population in the department. Because Cuvette Centrale is a department with an area of 48,250 km^2 and three general hospitals within a radius of 100 km, consanguineous marriage is prohibited. The prevalence of the sickle cell trait in our study is similar to that of some authors, who reported a prevalence of the sickle cell trait in a range of 16 to 21%. This could be justified by the fact that these countries belong to the Central African zone [4, 5, 14, 15]. In contrast, other authors in West and East Africa reported lower prevalences than ours (5 to 12%). This may be justified by the fact that these areas are far from the epicenter of sickle cell disease, which is in Central Africa [6, 10, 12, 13, 28]. Much lower prevalences (0.08 to 3.8%) are reported in European and American studies [9, 21, 23–25, 31].

In light of our observations, screening for sickle cell disease should also be systematic upstream during the premarital check-up in order to provide couples at risk with appropriate genetic counseling to guide their choice. However, it would be advisable to supplement this study with molecular biology techniques which would provide additional information on the possible presence of other haplotypes in Congo due to migration flows.

5. Conclusions

This work made it possible not only to update data on sickle cell disease in the neonatal period but also to provide epidemiological characteristics within each department of Congo. Prevalence remains stationary for the sickle cell trait, while it is increasing for major sickle cell syndromes. This resumes the frequency of homozygous and heterozygous forms of sickle cell disease in the Republic of Congo. The increase can be explained by the existence of consanguineous marriages and the absence of HbS screening tests in some regions, as well as the use of the Emmel test in other departments of Congo, although this test is less reliable The implementation of a national

program leading to systematic neonatal screening will make it possible to identify and provide early care for newborns with homozygous forms of hemoglobin S, which is a guarantee of a better quality of life, by limiting infectious and vaso-occlusive complications. The study was conducted with the aim of making neonatal screening systematic. It is a project that needs funding to be sustainable.

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DETAIL

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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.

Helegbe, G. K., Aryee, P., & Baba, S. M. (2023). Preterm delivery and neonatal deaths among anaemic pregnant women in the bolgatanga metropolis of ghana. Anemia, 2023 doi:https://doi.org/10.1155/2023/9865224

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 p0.05). 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.

Kuriri, F. A., Ahmed, A., Alanazi, F., Alhumud, F., Hakami, M. A., & Osama Atiatalla, B. A. (2023). Red blood cell alloimmunization and autoimmunization in blood transfusion-dependent sickle cell disease and β-thalassemia patients in al-ahsa region, saudi arabia. Anemia, 2023 doi:https://doi.org/10.1155/2023/3239960

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.

Mou, J., Zhou, H., Feng, Z., Huang, S., Wang, Z., Zhang, C., & Wang, Y. (2023). A case-control study of the factors associated with anemia in chinese children aged 3–7 years old. Anemia, 2023 doi:https://doi.org/10.1155/2023/8316658

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.

Wiafe, M. A., Ayenu, J., & Eli-Cophie, D. (2023). A review of the risk factors for iron deficiency anaemia among adolescents in developing countries. Anemia, 2023 doi:https://doi.org/10.1155/2023/6406286

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.

Olufemi-Aworinde, K., Olutogun, T. A., Akande, J. O., Akande, R. O., Odeyemi, A. O., Idowu, O. J., . . . Ala, O. A. (2022). The prevalence and pattern of anaemia in type 2 diabetics in ogbomosho, an urban community in

southwestern nigeria. Anemia, 2022 doi:https://doi.org/10.1155/2022/7650015

Anaemia is a frequent finding in type 2 diabetes, but it is typically seen with established chronic kidney disease and renal insufficiency. Cases, where anaemia predates renal insufficiency, are associated with a worse prognosis for the type 2 diabetes patient and an increased susceptibility to complications. This study aims to determine the prevalence and type of anaemia in persons living with type 2 diabetes without established chronic kidney disease in our environment. The study was a hospital-based cross-sectional study that involved 141 people with known type 2 diabetes as the study group and 140 healthy persons as controls. The study population and the controls were selected using a multistage sampling technique. Data were collected using an interviewer-administered semistructured questionnaire at the Endocrinology clinic, Bowen University Teaching Hospital, Ogbomosho. The data obtained were analyzed using the IBM SPSS version 23.0 (p value ≤0.05 was considered significant). The biochemical (fasting lipids, HBA1C, FBG, serum albumin, creatinine, urea, uric acid, and insulin) and haematological (FBC and red cell indices; PVC, MCV, MCH, MCHC, and RCDW) parameters of the respondents were analyzed using standard methods. The study showed a statistically significant difference in the prevalence of anaemia among subjects, 69.2% as compared to 30.8% of the control group. Normochromic normocytic anaemia was predominant among the subjects, whereas microcytic hypochromic anaemia was the predominant type in the controls. There was no statistically significant difference between MCV and MCHC of both subjects and controls. There was a positive correlation between the incidence of anaemia and the duration of diabetes among the subjects. More people with type 2 diabetes are now living longer, and the addition of haematological parameters should be part of their baseline investigations to aid in the early detection of complications.

Sisay, E. T., Aregash, A. Z., Tefera, C. M., Tadesse, A. W., Fozia, M. H., Feleke, Y. W., . . . Fanos, Y. A. (2022). Burden and determinants of anemia among under-five children in africa: Systematic review and meta-analysis. Anemia, 2022 doi:https://doi.org/10.1155/2022/1382940

Introduction. Globally, anemia among under-five children is a serious public health problem. Even if there are pocket studies here and there, there is limited evidence on the pooled prevalence of anemia among under-five children in Africa. Therefore, the aim of this study was to determine the pooled prevalence and determinants of anemia. Methods and Analysis. This systematic review and meta-analysis was done following the PRISMA guidelines. A comprehensive search was made in PubMed/MEDLINE, Cochrane Library, HINARI, and Ethiopian Journal of Health Development for studies published since 2009. It was supplemented with Google Scholar search. Study selection, data extraction, and quality of studies were assessed by eight reviewers. The Cochrane Q test and I2 test statistic were used to test the heterogeneity of studies. A random-effects model of DerSimonian-Laird method was used. Result. A total of 37 articles were included in this systematic review and meta-analysis. The pooled prevalence of anemia among under-five children in Africa was 59% (95% CI: 55, 63). Being female (AOR = 0.71; 95% CI: 0.57, 0.87), maternal education (AOR = 1.47; 95% CI: 1.31, 1.66), residence (AOR = 0.80; 95% CI: 0.67, 0.95), and family size (AOR = 0.93; 95% CI: 0.89, 0.98) were the determinants of anemia among African under-five children. Conclusion and Recommendation. This pooled study revealed that anemia was a severe public health problem. Sex, maternal education, residence, and family size were the determinants of anemia. Therefore, anemia prevention strategy should include sex consideration, educating mothers through youth education, area specific intervention, and encouraging birth spacing.

Thi, T. N., Tran, T. H., Thanh, D. T., Le, T. P., Nguyen, P. D., Tran, M. A., . . . Van, K. T. (2022). Molecular characterization and genotype-phenotype correlation of G6PD mutations in five ethnicities of northern vietnam. Anemia, 2022 doi:https://doi.org/10.1155/2022/2653089

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