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Original Article

Haemoglobin cut-off values for the diagnosis of anaemia in preschool-age children

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Abstract: Background: The World Health Organisation (WHO) suggests haemoglobin that (Hgb) cut-off levels below 2SD from the population mean to initiate anaemia investigations. In the absence of epidemiological data, Hgb less than 11 g/dL is considered abnormal in children up to the age of 59 months (4 years and eleven months). Objectives: This study reports on the Hgb cut-off levels among children at 1 and 4 years of age. The study compared the prevalence based on the WHO generic cut-off levels and population-specific cut-off-based value defined as below 2SD from the population mean. Design, settings, and Participants: A cross-sectional record-based study of healthy children below the age of 59 months attending primary care settings in Qatar. 3 years of Hgb data were collected and analysed using descriptive analyses. We excluded children with any pre-existing disease or who have altered biological parameters indicating a non-healthy child. Results: 39407 Participants were stratified into different sub-groups according to age, gender, and ethnicity. Hgb levels were expressed as the mean ± 2SD for children of one and four years of age. Most children were from Western Asia (45.6%), followed by Northern Africa (23.7%), and Southern Asia (21.7%). Our findings for one-year-old children cut-off levels for anaemia might be as low as 9.9 g/dL and 10.6 g/dL for 4-years old. Conclusion: Hgb cut-off values may be set at higher levels for one-year and four-year age groups and many different ethnicities. Higher cut-off points may overestimate the problem as a public health issue. Children may be unnecessarily treated with iron or have needless investigations.

Keywords: Cut-off levels, anaemia, diagnosis, children, paediatric

Introduction

Anaemia in preschool-age children is a leading cause of non-fatal health outcomes and years lost due to disability (YLD) [1, 2]. Though the full effect of anaemia on morbidity and mortality is challenging to establish, it is well known that childhood anaemia is associated with impaired child growth and poor cognitive abilities [3]. Haemoglobin (Hgb) level is considered the gold standard for assessing anaemia in preschool-age children.

To define anaemia and its severity, the WHO suggests Hgb cut-off levels below two standard deviations (SD) from the population mean. These cut-off levels are used to initiate anaemia investigations as they vary with age, gender and population. Despite the variation in Hgb cut-off levels with age, the WHO suggests a universal cut-off value of 11 g/dL up to the age of 59 months, independent of gender and age groups [4]. The absence of population-specific cut-off values have implications for estimating the prevalence of anaemia and disease burden. Higher cut-off points may overestimate the problem. Therefore, it is essential to define Hgb cut-off levels to report prevalence of anaemia accurately. Moreover, it has implications for the diagnosis and management of anaemia in children.

US and Australia have updated age-specific cut-off levels in children up to the age of two years [5-7]. In comparison, Canada and the UK utilise WHO cut-off levels [8-10]. Conducting prevalence studies using WHO cut-off levels may misrepresent disease burden and result in overdiagnosis, unnecessary investigations, and treatment in critical age groups. Therefore, it is essential to establish and implement population-specific cut-off levels.

In Qatar, WHO cut-off levels are used. Population-specific cut-off level has not been established. This study was undertaken to estimate the mean Hgb concentrations among pre-school-age children and propose a population-specific cut-off level to diagnose anaemia by age, gender and nationality in Qatar. These findings will help improve primary care and public health practice related to the diagnosis and management of anaemia in children residing in the country.

Methods

Study setting, design and population

The study was conducted in Primary Health Care Corporation (PHCC), the largest publicly funded primary health care service provider in Qatar. It has twenty-seven health centres distributed across the country. All pre-school children age (below 59 months) residing in Qatar are registered with PHCC. Anaemia screening is recommended for children at 12 months of age.

A cross-sectional study was designed. Data were extracted from PHCC's electronic medical records (EMR) for a period of three years (2016-2019). Population meeting the following criteria were included 1) aged below 59 months of age and 2) had a medical encounter and an Hgb test result recorded. A total of 117,751 medical encounters matched the criteria for inclusion in the study. These data were restructured using the specific individual as the sampling units with many possible medical encounters in a paired structure. If a specific child's medical encounters were more than 11 months apart, they were included in the database as new records.

Individuals with a diagnosis of anaemia other than nutritional anaemia (iron deficiency anaemia) were excluded from the database (See appendix). Only individuals aged one year (9 months to 15 months of age allowing an interval of +/- 3 months to the exact 12 months age) and four years (45-51 months of age allowing an interval of +/- 3 months to the exact 48 months age were included. These two age groups were selected because they represent Qatar's population based on PHCC's policy is to routinely screen them.

The variable list included demographics, past medical history, and blood investigations. Demographics included gender and nationality. Nationality was classified into categories (See appendix). The Hgb concentration was analysed for 'assumed healthy' children. Healthy children were defined as those with no nutritional anaemia or abnormal laboratory test results, namely: abnormal liver or kidney function test, erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP) or leukocytes (WBC) levels.

Statistical analysis

Descriptive statistics of the mean minus two Standard Deviation (SD) were used to define the anaemia cut-off level for diagnosis in different age groups. Participants included in the study were stratified into different sub-groups according to age, gender, and nationality (nationalities were grouped into categories) and cut-off levels were reported by them. The prevalence of anaemia was reported by population-specific cut-off values and compared to internationally agreed values. Hgb concentrations were expressed as means ± SD for the following two age groups:

- 1 Year of age +/- 3 months (9-15 months).
- 4 years of age +/- 3 months (45-51 months).

Frequencies were presented as percentages (%) and 95% confidence intervals (CIs). A *p*-value less than ≤ 0.05 (typically ≤ 0.05) is considered significant. Data analysis was carried out using the statistical package IBM SPSS statistics software (SPSS) version 26.0. The 3rd and 97th centile cut-off points (which correspond to the mean +/- 2 standard deviation) were calculated for all strata.

Ethical approval

The study was approved by the Research-Subcommittee of the PHCC before its initiation (Ref No. PHCC/RS/19/04/005). No informed consent was required since anonymised electronically stored data were used. Data were encrypted on storage, and only principal investigators had access to the database.

Results

Population characteristics

A total of 39,407 children aged 1 (67.6%) and 4 years old (32.4%) with valid Hgb measurements recorded in the EMR were included in the an-

Table 1. Population characteristics

	N	%
Age group (+/- 3 months)		
one year	26653	67.6
4 years	12754	32.4
Total	39407	100.0
Sex		
Female	19469	49.9
Male	19938	50.1
Total	39407	100
Nationality		
Northern Africa	9313	23.7
Sub-Saharan Africa	709	1.8
Latin America and the Caribbean	60	0.2
Northern America	669	1.7
Central/Eastern Asia	38	0.1
South-eastern Asia	1653	4.2
Southern Asia	8561	21.7
Western Asia	17965	45.6
Europe	366	0.9
Australia and New Zealand/Melanesia/Micronesia/Polynesia	32	0.1
Total	39366	100.0

alysis. Males constituted half of the sample (50.1%). The highest proportion of children were from Western Asia (45.6%), followed by Northern Africa (23.7%) and Southern Asia (21.7%) (see **Table 1**). 3.5% of the study population was pre-diagnosed with nutritional anaemia and 0.6% had at least one abnormal laboratory test value (abnormally high serum CRP, blood ESR, Hgb F, serum ALT, AST, blood urea and creatinine) (see **Table 2**). No obvious or significant differences in the mean Hgb concentrations were seen in healthy children compared to children with nutritional anaemia or those with laboratory test abnormalities (see **Table 3**).

Mean Hgb concentrations and cut-off levels

The mean Hgb concentration for children aged one year was 11.8 gm/dl with a normal range of values (mean +/- two standard deviations) ranging between 9.8 gm/dl and 13.8 gm/dl (see **Table 4**). The cut-off value for the diagnosis of anaemia should be set at < 9.8 gm/dl in children aged 1-year-old in Qatar (considering the statistical cut-off value for anaemia as < 3rd percentile is almost similar < 9.9 gm/dl). The gender effect is minimal and insignificant when compared at the 95% confidence interval for the mean.

South-Eastern Asians were associated with the highest mean Hgb of 12.3 gm/dl, while North Africans were associated with the lowest mean of 11.6 gm/dl. This effect of nationality on mean blood Hgb of healthy children is also reflected in a similar pattern for setting the cut-off value for diagnosis of anemia. Higher cut-off values (10.6 gm/dl) would apply to South Eastern Asian nationality and lower ones (9.5 gm/dl) apply to Northern Africa.

The mean Hgb concentration for children aged four years was 12.2 gm/dl with a standard range of values (mean +/- two standard deviations) ranging between 10.6 and 13.8 gm/dl. The cut-off value for the diagnosis of anaemia would be set at < 10.6 gm/dl for healthy children residing in Qatar in this age group (considering the statistical cut-off value for anaemia as < 3rd percentile is almost similar < 10.7 gm/dl. Like the one-year-old group, gender effect is very small and insignificant compared to the 95% confidence interval for the mean. Besides, South Eastern Asian nationality was associated with the highest mean blood Hgb of 12.7 gm/dl, while European nationality was associated with the lowest mean of 12 gm/dl. This effect of nationality on mean blood Hgb of apparently healthy children is also reflected in a similar pattern for setting the cut-off value for diagnosing anemia (see **Table 4**).

Discussion

This study is the first to establish the mean of Hgb concentrations among preschool-age children residing in Qatar. It was found to be 11.8 gm/dl for children aged one year and 12.2 gm/dl for children aged four years. The cut-off value for defining anemia in one- and four-year-old children residing Qatar was 9.8 and 10.6 gm/dl respectively. These cut-off values are significantly lower than those proposed by WHO/

Table 2. Pre-diagnosed nutritional anaemia and abnormal laboratory results

Total N = 39407	N	%
Pre-diagnosed with nutritional anaemia	1362	3.5
Abnormally high serum CRP (cut-off value = 5)	42	0.1
Abnormally high blood ESR (cut-off value = 20)	46	0.1
Abnormally high blood Hgb F (cut-off value = 5% for age 1+ year)	23	0.1
Abnormally high serum ALT (cut-off value = 28)	83	0.2
Abnormally high serum AST (cut-off value = 60)	27	0.1
Abnormally high blood urea (cut-off value = 6.5)	31	0.1
Abnormally high serum creatinine (cut-off value = 39)	45	0.1
At least one abnormally high measurement (from the above list of 7 tests)	255	0.6

Table 3. Mean study sample Hgb concentration (gm/dl) in one and four year olds with or without pre-diagnosed nutritional anaemia and abnormal laboratory test values

	Blood Hgb conc (g/dL)						
	Range	Mean	95% confidence interval of the mean	SD	SE	N	(3rd-97th centile)
One year old							
Pre-diagnosed nutritional anaemia/abnormal lab values							
Included	(18-5.6)	11.8	(11.8-11.8)	1.1	0.006	26653	(9.7-13.6)
Excluded	(18-5.6)	11.8	(11.8-11.8)	1	0.006	25552	(9.9-13.7)
4 years old							
Pre-diagnosed nutritional anaemia/abnormal lab values							
Included	(16.1-5.7)	12.1	(12.1-12.1)	0.9	0.008	12754	(10.5-13.8)
Excluded	(16.1-5.7)	12.2	(12.1-12.2)	0.8	0.008	12251	(10.7-13.8)

AAP (< 11 gm/dl for both age groups), Australia (10.5 gm/dl) and the UK (11.5 gm/dl).

The findings of this study show that applying the proposed cut-off values to calculate anaemia prevalence rates by gender and nationality show significant differences between subgroups. Males had a higher prevalence rate of anemia (4.2%; CI 3.9-4.6) in children aged one year compared to females (2.5%; CI 2.3-2.8). The sex differences were marginally different in children aged four years (Males-2.8%; CI 2.4-32 and Females-3%; CI 2.6-3.4). Variation in anemia prevalence rates were also seen between nationality groups. Northern Africans had the highest prevalence rate of 5.6% CI 5.1-6.2) and Europeans with the lowest rate of 0.7% (CI 0.1-2.1) in children aged one year. On the other hand, Sub-Saharan Africans had the highest prevalence rates of 6.4% (CI 2.9-12.2), while South-Eastern Asians had the lowest rates of 0.8% (CI 0.2-2.6) different in children aged four years.

A WHO systematic review published in 2005 reported an anaemia prevalence rate of 47.4% (95% CI 45.7%, 49.1%) in preschool-age children with nearly 293 million children affected [11]. The WHO anaemia prevalence report used predefined Hgb concentrations to assess prevalence based on two facts [5]. First, the cut-off values were used in previous WHO publications and second that the values were validated in 1989 by Second National Health and Nutrition Examination Survey (NHANES II) [12, 13]. The survey published in 1989 used NHANES II survey data from 1976-1980.

The original NHANES II survey used the age-specific fifth centile values for healthy persons. It excluded persons who are likely to have iron-deficiency anaemia based on iron parameters. Limitations of the report were that it had no data for children less than one year of age. Furthermore, it only included US citizens and did not report on ethnic variance. The current cut-off values used worldwide have been used since the sixties and possibly based on historical data specific to the US population.

Applying proposed cut-off values in Qatar, the anemia prevalence rate is estimated to be 3.4%

Table 4. Mean Hgb concentration (gm/dl) in healthy one and four years old age groups by nationality and gender

Excluding Pre-diagnosed nutritional anaemia/ Abnormal lab values	Range	Mean	95% confidence interval of the mean	SD	SE	N	(3rd-97th centile)
One year old							
Northern Africa	(16.4-6.6)	11.6	(11.6-11.7)	1.1	0.014	6004	(9.5-13.6)
Sub-Saharan Africa	(14.9-8.5)	11.8	(11.7-11.9)	1	0.042	579	(9.9-13.8)
Northern America	(15.1-9.6)	12	(12-12.1)	0.9	0.038	524	(10.4-13.7)
South-Eastern Asia	(16.1-5.6)	12.3	(12.2-12.3)	1	0.026	1389	(10.6-14.1)
Southern Asia	(18-6)	11.7	(11.7-11.8)	1	0.012	6914	(9.7-13.5)
Western Asia	(17.4-6.8)	11.9	(11.9-12)	0.9	0.01	9722	(10.1-13.7)
Europe	(15.3-9.3)	12	(11.9-12.1)	0.9	0.051	293	(10.5-13.7)
Other nationalities	(14.8-8.6)	12	(11.8-12.3)	1.1	0.112	99	(9.6-14.2)
Female	(17.4-6.1)	11.9	(11.8-11.9)	1	0.009	12731	(10-13.7)
Male	(18-5.6)	11.8	(11.8-11.8)	1	0.009	12821	(9.7-13.7)
Total	(18-5.6)	11.8	(11.8-11.8)	1	0.006	25552	(9.9-13.7)
95% confidence interval of Hgb values = (9.8-13.8)							
4 years old							
Northern Africa	(15.4-9)	12.2	(12.1-12.2)	0.8	0.015	2777	(10.7-13.8)
Sub-Saharan Africa	(14.5-9.1)	12.2	(12-12.3)	0.9	0.088	103	(10.4-13.4)
Northern America	(14.2-10.4)	12.4	(12.2-12.5)	0.8	0.069	123	(10.8-13.8)
South-eastern Asia	(15.3-10.4)	12.7	(12.6-12.8)	0.8	0.053	244	(11.2-14.3)
Southern Asia	(14.9-5.7)	12.1	(12.1-12.2)	0.9	0.026	1231	(10.6-13.8)
Western Asia	(16.1-7.4)	12.1	(12.1-12.2)	0.8	0.01	7671	(10.6-13.7)
Europe	(13.7-9.7)	12	(11.8-12.2)	0.8	0.106	64	(9.9-13.6)
Other nationalities	(14-10.1)	12.3	(12-12.7)	0.9	0.179	27	(10.1-14)
Female	(16.1-5.7)	12.2	(12.2-12.2)	0.8	0.011	6020	(10.7-13.8)
Male	(15.4-6.4)	12.1	(12.1-12.2)	0.8	0.011	6231	(10.6-13.8)
Total	(16.1-5.7)	12.2	(12.1-12.2)	0.8	0.008	12251	(10.7-13.8)
95% confidence interval of Hgb values = (10.6-13.8)							

for children aged one year. This rate is underestimated by a factor of 5.7 and 2.9 times in comparison to WHO/AAP and Australian/UK cut-off values, respectively. Similarly, applying the proposed cut-off values, the anemia prevalence rate is estimated to be 2.9% for children aged four years. This rate is underestimated by a factor of 2.8 and 7.9 times in comparison to WHO/AAP and Australian/UK cut-off values, respectively. These findings highlight the importance of defining cut-off values for specific populations rather than generalizing those developed using others.

Hgb is affected by age, sex, and ethnicity, among other factors [15]. These factors need to be accounted and adjusted for when determining that a child is anaemic. Different reports suggested that the current age-specific Hgb cut-off of 11.0 g/dL based on historic data [15-17] are due to a lack of supportive data. Similarly, there are variations across countries.

The World Development Indicators Databank report suggests a broad range of anaemia prevalence. US anaemia prevalence was reported to be the lowest at 8.5%, and Yemen reported as the highest at 86.2%. While one cannot deny the health disparities worldwide, the difference might be because of generic non-specific cut-off values to those populations. Studies recognise that the studies included were limited, and their estimates may not capture the full variations [18]. It is important to note that out of the 4372 studies in that dataset, 3802 of the studies did not report the mean Hgb concentrations in the population. The Hgb mean concentrations in 908 studies was 11.0 g/dL suggesting that 2SD should be significantly lower.

Implications for clinical practice and future research

The study findings suggest that current Hgb cut-off values may be set at lower concentrations for one-year (10 g/dL) and four years (10.5 g/dL) age groups and many different ethnicities. The results have implications for both public health planning as well as individual treatment. Setting a population sensitive cut-off value for defining anaemia has implications for reporting prevalence data, setting guidelines, and treatment decisions on individual concentrations. Higher cut-off points may overestimate the problem as a public health issue, and children may be unnecessarily treated with iron or have needless investigations. One could estimate that 15% of the study population at one year of age or 5% of the four-year age group have received treatment or investigations unnecessarily. There is a need to revaluate anaemia in preschool-age children in Qatar using the proposed Hgb cut-off values. Further studies with alternate designs are necessary to confirm support findings.

The primary challenge for conducting population-level studies is the availability of centralised databases. Countries with centralised electronic databases should prioritise cross-sectional record-based study to define population-specific cut-off Hgb levels for anaemia diagnosis in preschool-aged children, and prevalence studies should follow to assess disease burden and inform healthcare policies. A key component of study design is defining a healthy population. Researchers should prioritise the exclusion of patients with medical conditions that would affect their Hgb concentrations to be considered within the normal range [19].

With current screening recommendations in Qatar, there is a need to focus on preschool-age children. The results would help form the basis for further research into causes of anaemia in this age group and others that are population specific.

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Disclosure of conflict of interest

None.

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