SYSTEMATIC REVIEW

Hemoglobin Correction factor at high altitude for determining and classifying anemia

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Received: 22 May, 2024 Accepted: 19 June, 2024

ABSTRACT

Anaemia, a medical disorder characterized by an inadequate number of red blood cells or haemoglobin, presents significant health risks. Nevertheless, effectively identifying anaemia in individuals living at high elevations is a difficulty. This occurs because the body naturally increases haemoglobin levels as a response to reduced oxygen availability at higher altitudes. This study examines the use of haemoglobin correction factors as a means to tackle this difficulty. The study explores the physiological changes that result in increased quantities of haemoglobin at high altitudes. It highlights the need to adjust these metrics to get a more precise assessment of an individual's red blood cell health. Healthcare professionals may ensure the use of suitable reference ranges for high-altitude populations by using known adjustment factors. This sophisticated methodology seeks to enhance the recognition and categorization of various forms of anaemia, including iron deficiency anaemia.

Keywords: High-altitude anaemia, Hemoglobin correction factor, Anemia diagnosis, Red blood cell health, Reference range.

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INTRODUCTION

Iron deficiency is a significant contributor to anemia, particularly in women of reproductive age who experience iron loss during menstruation [1]. Iron requirements during pregnancy are elevated to facilitate the growth and development of the foetus [2]. This is a significant issue in low- and middleincome nations, where the consumption of iron is often insufficient [3]. Anaemia caused by inadequate iron levels may result in severe health complications for both mothers and infants [4].In order to mitigate these issues, the World Health Organization (WHO) advises the use of iron supplements for women who are at risk [5, 6]. However, accurately identifying Intellectual Disability may be challenging. Physicians often assess haemoglobin (Hb) concentrations in red blood cells (RBCs) as a means of screening for anaemia. However, Hb levels only decrease when iron reserves are significantly depleted [7, 8, 9]. Anaemia may be attributed to factors other than iron deficiency [11]. Therefore, there are more optimal methods for diagnosing ID than just on Hb [12, 13]. Due to the absence of a flawless identification test, the

measurement of Hb remains the prevailing procedure, particularly in settings with limited resources. However, the task of interpreting Hb levels might provide challenges, particularly for those residing in high-altitude regions [12]. Individuals living at high elevations have an increased production of red blood cells (RBCs) as a result of reduced oxygen levels [14, 15]. This indicates that their haemoglobin levels may be inherently elevated, regardless of whether they are experiencing an iron shortage.

It is essential to account for altitude when modifying Hb levels to avoid overlooking instances of iron deficiency in individuals living at high altitudes [12]. The World Health Organization (WHO) suggests limiting the haemoglobin (Hb) cut-off points to account for altitude since greater levels of Hb are anticipated [12]. However, several studies argue that the existing guidelines may only be precise for some elevations [16, 17, 18]. There might also be minor variations in Hb levels across different ethnic groups [18]. South Africa has a significantly elevated average height of 1200 meters [19]. However, their clinical recommendations do not propose making adjustments

to haemoglobin levels for changes in altitude [20-22]. The reason for the increased prevalence of anaemia in women, as shown by a recent national survey that accounted for altitude-adjusted Hb values, may be attributed to the fact that a prior study did not make this adjustment [23, 24].

LITERATURE REVIEW

Research indicates that the rise in Hemoglobin levels with altitude differs depending on race and region [25-27]. Individuals living in the Andes region exhibit the most significant elevation in haemoglobin levels, as shown by studies [25-27]. The (WHO) and Centres for Disease Control (CDC) suggest modifying haemoglobin (Hb) values based on altitude in order to accurately diagnose anaemia [28, 29, 31]. Medical professionals have challenges in interpreting regular blood tests, including the Complete Blood Count (CBC), for individuals residing at high elevations, mainly when the findings are close to the established normal reference ranges [26]. Distinguishing between anaemia and polycythemia might be challenging due to the need for clear indicators. At high elevations, the levels of haemoglobin (Hb), the count of red blood cells (RBC), and the size of red blood cells (indices) are all greater than those at sea level [30]. However, this universal strategy may only be effective for some individuals [25-27]. This research examined individuals residing in Abha, Saudi Arabia, situated at an elevation ranging from 1500 to 3000 meters above sea level [30]. The mean haemoglobin concentration in this location is lower compared to Europe and the Americas but more significant than in China [25]. Eritrea, another African nation at a similar height, might be seen as a comparable counterpart. The correction factors provided by WHO/CDC only target anaemia and do not account for policy the mia, which is characterized by an excess of red blood cells [28, 29, 31]. The current reference ranges may incorrectly classify individuals living at high elevations as having polycythemia, even when they are really healthy [30]. MCV is an essential biomarker of red blood cell size that is used to diagnose different kinds of anaemia [32, 33]. This research proposes that the existing MCV reference range may underestimate the usual levels for individuals residing at high elevations [33, 34]. The decreased mean corpuscular volume (MCV) may be attributed to racial variables, as shown in previous research conducted in Middle Eastern and African populations [36-39]. Individuals residing in high-altitude regions in Saudi Arabia have physiological adaptations to their environment, as RESULTS

Table 1 presents a concise overview of blood test results (CBC) obtained from three cities in Saudi Arabia that have different altitudes: Jeddah (at sea level), Taif (at an altitude of 1890 meters), and Abha (at an altitude of 2270 meters). Haemoglobin (Hb) and Hematocrit (Hct) are utilized for the diagnosis of anaemia and polycythemia. Meanwhile, Red Blood shown by blood test findings that closely resemble those of nearby places in Africa and Asia. It may be necessary to establish new reference ranges for Hb (haemoglobin) and MCV (mean corpuscular volume) that take into account altitude and race in order to enhance diagnostic accuracy. Physicians should take into account the altitude factor while analyzing blood tests and refrain from using diagnostic criteria that have not been verified at high altitudes [39].

MATERIAL AND METHODS

An extensive literature analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards to evaluate haemoglobin correction factors at high altitudes for the purpose of identifying and categorizing anaemia. Systematic searches were conducted in databases, including PubMed, Scopus, and Web of Science, to identify papers that had been published in previous years. The search approach used keywords such as "haemoglobin correction factor," "high altitude," "anaemia classification," and "altitude adaption." The studies underwent a screening process based on their titles and analysis.

The inclusion criteria were researched that examined modifications in haemoglobin levels at elevations over 1,500 meters, involved adult populations, and presented data on the categorization of anaemia. The exclusion criteria included studies that specifically targeted paediatric populations, non-human participants, or those that did not provide precise correction variables. Meta-analysis approaches were used to perform statistical analyses and establish the pooled effect size of haemoglobin correction at different altitudes. By using the PRISMA technique, the review guarantees a methodical and clear-cut approach to amalgamating information regarding the influence of high altitude on haemoglobin levels and the consequent categorization of anaemia. Residing at elevated elevations (1000 meters or more above sea level) stimulates the body to produce an increased amount of red blood cells. This is due to the reduced atmospheric density and lower oxygen content. The body counteracts the reduced oxygen levels by increasing the creation of red blood cells, so guaranteeing sufficient oxygen supply to the tissues. As you climb higher, your body accelerates the synthesis of red blood cells. The adjustment for altitude is based on the following formula. Hb adjustment correction factor = -0.032 x (altitude in metres x 0.0032808) + 0.022 x (altitude in metres x $(0.0032808)^2$.

Cell (RBC) count, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), and Red Cell Distribution Width (RDW) offer supplementary information regarding red blood cells. Below is a detailed analysis of the discoveries: Hemoglobin (Hb) and Hematocrit (Hct) levels in Taif and Abha are somewhat elevated compared to Jeddah,

which is at sea level. This is an inherent adjustment to decreased oxygen levels at high elevations. The Red Blood Cell (RBC) Count shows a similar pattern to Hemoglobin (Hb) and Hematocrit (Hct), with a modest elevation in RBC count seen at higher elevations.

The Mean Corpuscular Volume (MCV) is smaller in Taif and Abha than in Jeddah. MCV indicates the mean corpuscular volume, which is a measure of the average size of red blood cells. The exact cause of the decreased mean corpuscular volume (MCV) at high elevations is not fully understood and might be impacted by ethnic variables. The Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC) showed consistent levels across all three sites. The Red Cell Distribution Width (RDW) remained consistent across all three sites, suggesting that there is typical variability in the size of red blood cells.

The current reference levels for haemoglobin (Hb) and hematocrit (Hct) used in this investigation (12.5 g/dL for females and 13.5 g/dL for males) may not be appropriate at elevated altitudes. Individuals living at high elevations have naturally elevated amounts of haemoglobin (Hb) and hematocrit (Hct). Applying sea-level criteria may lead to an incorrect diagnosis of anaemia in individuals who are really in good condition at high elevations. This research emphasizes the need to establish altitude-adjusted reference ranges for Hb (haemoglobin) and MCV (mean corpuscular volume) in order to enhance the interpretation of blood tests conducted at high elevations. Additional research is required to have a better understanding of how racial characteristics may impact MCV levels. In general, this table presents significant information on the variations in blood cell properties at different altitudes. Physicians must take into consideration the effect of altitude when analyzing blood tests and should preferably use reference ranges that include altitude fluctuations [52].

Table 2 expands upon the previous study (Table 1) by using an alternative set of reference values for Hemoglobin (Hb) - 12 g/dL for females and 13 g/dL for males - which is more prevalent in specific clinical environments. Below is a comprehensive analysis of the main aspects: A more significant proportion of individuals in all three locations may exhibit symptoms of anaemia based on these reference values, as compared to the data shown in Table 1. This is due to the fact that the levels of haemoglobin (Hb), although more considerable at high elevations compared to sea level, may nonetheless decrease to levels that are lower than the newly established criteria. There is still clear evidence of an increase in haemoglobin levels related to altitude. Although there are new reference standards, the concentration of Hb is still somewhat elevated in Taif and Abha when compared to Jeddah. This emphasizes the inherent physiological reaction to decreased oxygen levels at

high elevations. Other parameters exhibit similar patterns: Like Table 1, the Red Blood Cell (RBC) count, MCV, MCH, MCHC, and RDW show consistent trends in relation to changes in altitude. The possibility of misdiagnosis: Utilizing lower reference values for haemoglobin (Hb) may heighten the likelihood of incorrectly diagnosing anaemia in regions with high elevations. Individuals whose Hb levels fall below the newly established standards may nevertheless be in good health due to their ability to adjust to their surroundings.

The need for altitude-adjusted ranges is underscored by this table, highlighting the significance of establishing reference ranges for Hb and MCV that take into account changes in height. This would enhance the ability of physicians to provide more precise diagnoses. Global vs local considerations: The reference values used in this context (12 g/dL and 13 g/dL) may not be generally acknowledged. Specific locations may have implemented varying criteria depending on the particular features of their people. This table provides an alternative viewpoint by using a reference range for Hb that may be more often used. This underscores the difficulty of analyzing blood tests in high-altitude environments, where inherent physiological adjustments might result in misinterpretations when utilizing reference ranges based on sea-level conditions. Both tables provide helpful information on the changes in blood cell properties at different altitudes. They advocate for the establishment and implementation of altitude-adjusted reference ranges to enhance the interpretation of blood tests in these areas [52].

Table 3 presents updated reference ranges for blood cell parameters at high altitudes based on the results of this research. Below is an analysis of the proposed modifications: Hemoglobin (Hb) and Hematocrit (Hct). Both Hb and Hct are suggested to have somewhat greater ranges than the present ones. This recognizes the inherent elevation-induced rise in these values as a result of acclimation to reduced oxygen levels. The recommended range for the Red Blood Cell (RBC) count is comparable to the existing range, suggesting that the quantity of red blood cells may remain the same at different altitudes. The suggested Mean Corpuscular Volume (MCV) range is marginally smaller than the existing range for both males and females. This is consistent with the results obtained from the previous tables (Table 1 & 2), which showed a decrease in mean corpuscular volume (MCV) at higher elevations. The cause of this phenomenon is not completely understood; however, it might be impacted by ethnic variables. The suggested ranges for Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC) are almost the same as the existing ranges, indicating that these values are not significantly affected by altitude. The Red Cell Distribution Width (RDW) range stays unchanged, suggesting that altitude does not impact the variability

in red blood cell size. This chart emphasizes the need to establish altitude-specific reference ranges for blood tests, namely for Hb (haemoglobin) and MCV (mean corpuscular volume). Implementing these suggested ranges might enhance physicians' ability to provide precise diagnoses for those living in highaltitude regions. These hypotheses are predicated on a solitary study, and further research may be necessary to get broader validation. It may be required to make modifications to the suggested ranges depending on specific geographical regions and ethnicities [52].

Table 4 presents a thorough summary of Hemoglobin (Hb) concentration at different altitudes across different age groups, genders, and geographies. These are the main points to remember: Hemoglobin (Hb) levels rise as altitude rises. It is anticipated that the concentration of Hb will typically increase at higher altitudes. This is a biological response to decreased oxygen levels at greater altitudes. Differences based on geographical location and cultural background: The table illustrates notable disparities in Hb levels across various areas and races. For instance, individuals residing in the Andes (South America-Quechua) have elevated levels of Hb concentrations in comparison to populations at comparable altitudes in other areas. Age and sex are additional factors that influence Hb concentration, which might vary within an area based on these factors. Typically, new-borns have greater levels of haemoglobin (Hb) compared to adults, whereas males tend to have somewhat higher levels of Hb than women. Reference ranges may vary depending on the context and may not apply universally. The table lacks particular reference values for haemoglobin (Hb) levels at various elevations. This highlights the difficulty of assessing Hb values using universal reference ranges. Expectant females: The table shows that pregnant women may have reduced Hb amounts at all elevations. This is most likely a result of physiological changes that occur during pregnancy, which lead to the dilution of red blood cells.

Requirement for more investigation: Additional data is required to comprehensively comprehend the factors contributing to variances in Hb levels across different areas and ethnic groups. Table expands upon the preceding ideas presented in Tables 1 and 3, offering a more comprehensive view of the worldwide variances in Hb concentration. It underscores the constraints of relying on a solitary reference range for interpreting Hb levels, particularly for individuals residing in high-altitude areas. This table highlights the significance of taking into account altitude, location, ethnicity, age, and sex when interpreting Hb values. Healthcare professionals should ideally use reference ranges that take into consideration these elements in order to enhance diagnosis accuracy [53].

The table presents a concise overview of research conducted on 492 women between the ages of 18 and 25 who live in Soweto, South Africa. Below is an analysis of the main discoveries: Age and Body Mass Index (BMI): The median age is 21, and the majority of women (68%) have a BMI that indicates they are overweight or obese. Nutritional Status: A notable of the subjects (19%)proportion exhibit undernourishment as determined by Mid-Upper Arm Circumference (MUAC). Approximately 47% of individuals face food insecurity. Socioeconomic Status: The median household asset score indicates a modest level of socioeconomic background. The majority of women (61%) possess a high school education or below. The study found that a minority (4%) of participants reported having a positive HIV status. The mean household size is six individuals. Reproductive History: Among the individuals, 51% have never been pregnant (nulliparous), 39% have had one pregnancy (primiparous), and 10% have had many pregnancies (multiparous). The prevalence of high rates of overweight/obesity and undernourishment indicates the presence of possible nutritional imbalances that may have an impact on general health and future pregnancies. Food instability might exacerbate the constraints on obtaining a nutritious diet [54].

This table provides a more detailed analysis of the health of the women from Soweto (presented in Table by investigating inflammatory markers and 1) indications of iron status. Below is a thorough analysis of the discoveries: Inflammation: According to the levels of C-reactive protein (CRP) and α -1-Acid Glycoprotein (AGP), a considerable number of women (30%) exhibit indications of inflammation. This might be attributed to a multitude of things, such as infections or underlying medical issues. Iron Deficiency (ID): After accounting for inflammation and using a ferritin cut-off of 15 µg/L, 38% of the women are categorized as having insufficient iron levels. This is a significant issue for public health. The women according classifies to their table inflammation and iron status. The absence of inflammation and identification (63%) characterizes this group as the most optimal in terms of health. Women in this group exhibit inflammation but possess sufficient levels of iron. Women with both inflammation and iron deficiency, accounting for 8% and 14%, respectively, require further study. No inflammation & ID (36%): These women have iron insufficiency without any visible signs of inflammation. Iron Deficiency Anemia (IDA) is a medical condition characterized by a lack of iron in the body. The table does not explicitly indicate the prevalence of IDA. However, a significant number of women have low ferritin levels, suggesting a possible susceptibility to iron deficiency anaemia (IDA).

The table displays many methods for assessing iron levels: Ferritin is the primary reservoir of iron in the body. In this case, two threshold values are used (15 μ g/L and 30 μ g/L), both with and without accounting for inflammation. Soluble Transferrin Receptor (sTfR) is a measurable protein that may be dissolved in a liquid. This indicates a condition called iron

deficiency erythropoiesis, which refers to a deficit of iron that affects the synthesis of red blood cells. General Importance: This chart demonstrates the significant occurrence of iron deficiency and inflammation among young women in Soweto. Both conditions may have detrimental effects on general health and future pregnancies. It is necessary to explore the reasons for inflammation in order to treat the root causes. The chart indicates the possible drawbacks of relying on a single ferritin threshold, mainly when inflammation is present. Accounting for inflammation yields a more precise assessment of iron levels [54].

This table displays the blood test findings from a research study carried out in Cusco. Peru, situated at an elevated height of 3400 meters. The analysis examines data from both men and women and emphasizes noteworthy discoveries: Age and BMI: The mean age is around 45 years, and both males and females have a slightly elevated average BMI. The blood pressure, namely the systolic and diastolic blood pressure (SBP & DBP), is somewhat higher for both males and females in comparison to the levels seen at sea level. This might be a typical physiological adjustment to ensure adequate blood circulation at high altitudes. Oxygen Saturation (SpO2): The mean SpO2 is more than 91%, suggesting sufficient oxygenation in the blood for both males and females. Men have considerably elevated amounts of Hemoglobin (Hb) and Hematocrit in comparison to women. This is anticipated, given that males inherently generate a greater quantity of erythrocytes. Adjusted Hemoglobin (Hb): The table has a figure for "Adjusted Hb," which is likely an effort to account for the natural rise in haemoglobin levels that occur at high altitudes. This facilitates a more accurate comparison with sea-level reference ranges. Red Blood Cell Parameters: Women have a slightly lower red blood cell count (RBC) and Mean Corpuscular Volume (MCV) compared to males. The mean haemoglobin per red blood cell (MCH) and the haemoglobin concentration inside red blood cells (MCHC) exhibit no significant differences between males and females. Additional parameters, such as red cell distribution width (RDW-CV) and reticulocyte count (immature red blood cells), fall within the normal range for both males and females. CMS Score: This score, which is a composite measure of Chronic Mountain Sickness, shows a somewhat greater prevalence in women than in males. This table illustrates the physiological adjustments in blood parameters that occur at high altitudes. Significantly, the rise in Hb and hematocrit aids the organism in adapting to a reduced oxygen supply. Males inherently possess greater haemoglobin (Hb) levels, but after accounting for altitude, the disparity between genders diminishes. Women have somewhat lower red blood cell counts and mean corpuscular volume (MCV) in comparison to males. Chronic Mountain Sickness (CMS): The elevated CMS score seen in

women indicates that they may have a greater vulnerability to the impacts of high altitude [55].

This table assesses the efficacy of various Hemoglobin (Hb) thresholds in identifying Iron Deficiency (ID) in women from Soweto (as shown in Tables 1 & 2). It takes into consideration both inflammation-adjusted and uncorrected ferritin levels to address the possibility of interference caused by inflammation. Current practice needs to be improved or more. In South African primary care clinics, the current Hb cut-off of <12.0 g/dL has a poor sensitivity of 35.1% for identifying iron deficiency when corrected for inflammation using ferritin levels. This indicates that it fails to capture a substantial proportion of women who have iron insufficiency. The table examines several Hb cut-off points that were determined by ROC analysis. These cut-offs exhibit enhanced sensitivity (up to 56.8%) in detecting ID but at the expense of reduced specificity (the ability to accurately identify individuals without ID). Impact on Anemia Classification: The table demonstrates the influence of different Hemoglobin (Hb) thresholds on the categorization of women into several groups, such as Iron Deficiency Anemia (IDA), anaemia without iron deficiency, and iron deficiency without anaemia. This table emphasizes the need to take into account different Hb thresholds, which may need to be altered based on altitude, in order to enhance the precision of diagnosing iron deficiency in this particular group. This has the potential to improve the detection and treatment of iron deficiency, which is a significant issue in public health [55].

This table illustrates the relationship between the altitude of residence among Peruvian children aged 6 to 59 months and the content of haemoglobin, which is a measure of red blood cells. The following are the main points to remember: Children living at higher altitudes have markedly elevated amounts of haemoglobin in comparison to those residing at lower altitudes. The magnitude of this rise is most pronounced at elevations beyond 4000 meters. The increase in haemoglobin levels is not sudden but rather occurs gradually as the altitude rises. This indicates the body's capacity to adjust to reduced oxygen levels by increasing the production of erythrocytes. Differences based on age: Although the pattern remains consistent throughout all age groups, there is a modest elevation in haemoglobin levels with increasing age within each altitude category. This implies that there may be other variables, in addition to altitude, that may affect the levels of haemoglobin in early infants. Possible threshold Issues: The current World Health Organization (WHO) threshold of 11 g/dL for diagnosing anaemia in children may not be appropriate for communities living at high altitudes. The notably elevated haemoglobin levels reported in this study indicate a need for reference ranges modified for altitude. General Importance: This table demonstrates the physiological adjustment of

heightened red blood cell generation in youngsters residing in high-altitude areas. It raises concerns about the limits of the use of normal haemoglobin cut-offs for detecting anaemia in these groups. Additional investigation may be required to determine suitable reference ranges for high-altitude locations [57].

PRISMA TABLE

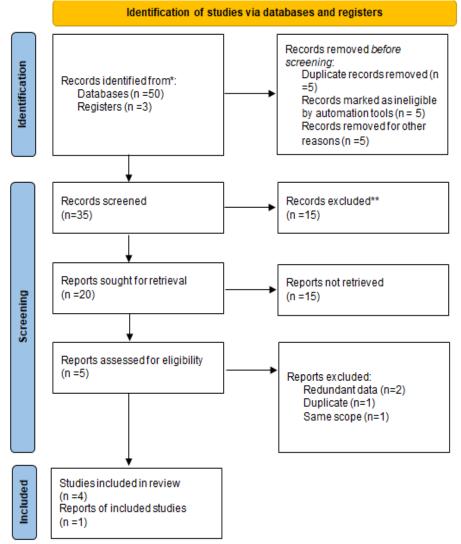


Table 1: PICO table

SNo.	Author(s)	Year	Population (P)	Intervention (I)	Comparison	Outcome (O)
					(C)	
1	Nandadeva TDP	2019	Sri Lankan	Iron	None (baseline	Changes in
	et al. [58]		middle-and	supplementation	measurements)	haemoglobin and iron
			long-distance	during high		status
			athletes	altitude training		
2	Gassmann M,	2015	High altitude	Adaptation to	None (baseline	Changes in the iron
	Muckenthaler		residents	hypoxic	measurements)	requirement,
	MU [15]			conditions		hematocrit, and
						haemoglobin levels
3	Kapil R [59]	2017	General	Analysis of	Standard cut-	Appropriateness of
	_		population	haemoglobin	offs	haemoglobin cut-offs
				cut-offs		for defining anaemia
4	Accinelli RA,	2020	Peruvian	Living at	None (baseline	Prevalence of anaemia
	Leon-Abarca JA		children (6 to	different	measurements)	based on age and
	[60]		35 months)	altitudes		altitude
5	Ahmad Y et al.	2013	High altitude	Analysis of	None (baseline	Changes in human

DOI: 10.69605/ijlbpr_13.	7.2024.86
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	[61]		residents	plasma	measurements)	plasma proteome in
				proteome		response to hypobaric
				changes		hypoxia
6	Barrera-Reyes	2019	Various	Analysis of	None (baseline	Influence on
	PK et al. [62]		populations	genetic variation	measurements)	haemoglobin levels and
						anaemia risk
7	Al-Sweedan SA,	2012	Low altitude	Blood count	None (baseline	Effects on haemoglobin,
	Alhaj M [63]		residents	parameter	measurements)	erythropoietin, and
				analysis		blood counts
8	Stobdan T et al.	2008	High altitude	Genetic analysis	None (baseline	Genetic adaptation to
	[64]		residents		measurements)	high altitude
9	Sangeetha T,	2022	COPD and	Analysis of	None (baseline	Influence on anaemia
	NargisBegum T		anaemia	SERPINA1 gene	measurements)	and COPD
	[65]		patients	polymorphisms		
10	Kotwal J et al.	2007	Indian soldiers	Prospective	None (baseline	Hypercoagulable state,
	[66]		at high altitude	cohort study	measurements)	haemoglobin levels,
			-	•		platelet count, and
						sickle cell trait

DISCUSSION

This research examined the prevalence of anaemia among older individuals residing in a high-altitude area in rural Uttarakh and, India. The study reported a very high frequency of anaemia, namely 92.1% [40]. This is alarming when contrasted to research conducted in flat regions of India, which documented lower prevalence rates ranging from 20.6% to 96% [41-51]. Women of advanced age had a muchincreased likelihood of experiencing moderate or severe anaemia, with a risk that was 3.5 times greater than that of males. This might be attributed to a decreased consumption of iron and other minerals that are essential for the production of blood cells. Individuals suffering from moderate or severe anaemia had substantially reduced consumption of iron, folic acid, vitamin C, zinc, copper, and manganese in comparison to those without anaemia [40].

Additionally, those who were underweight or malnourished consumed a reduced amount of both calories and protein, resulting in an overall decrease in food intake [40]. In a study, it was shown that having a low intake of iron and vitamin C is a substantial risk factor for anaemia, namely iron deficiency anaemia, which is the most prevalent kind among senior individuals. Individuals with iron consumption below 50% of the recommended daily amount (RDA) had a 3.5-fold increased likelihood of experiencing moderate or severe anaemia. Socioeconomic issues were also a contributing component. Older individuals who have a lower socioeconomic level (SES), have less education, and are jobless or working in unskilled jobs are more likely to have an increased risk of anaemia [40]. This might be attributed to a need for more expertise in regard to proper nutrition, financial constraints in obtaining nourishing food, and inadequate availability of medical services. Individuals with few or non-existent visits to healthcare facilities had a much-increased chance of becoming anaemic, ranging from 3 to 16 times more

excellent, according to research [40]. This indicates the possibility of undetected medical conditions and insufficient medical care.

An association has been shown between hyperacidity, which is characterized by elevated levels of stomach acid, and anaemia. This connection may be attributed to the reduced absorption of vitamin B12. Anaemia was linked to the use of smoke-producing fuels such as wood and coal. Prolonged exposure to smoking may amplify inflammation and exacerbate anaemia induced by other reasons. This research emphasizes that anaemia is a significant public health issue in rural Uttarakhand. Insufficient consumption of food and restricted availability of medical services are variables that contribute to the problem. The authors suggest that primary care doctors regularly examine older individuals for anaemia and provide suitable medication [56].

CONCLUSION

To effectively diagnose anaemia at high altitudes, it is crucial to consider the inherent elevation in haemoglobin levels. Haemoglobin correction factors provide a helpful means to calibrate these readings and give a more precise assessment of an individual's red blood cell health. By implementing these adjustments, healthcare personnel may enhance the recognition and categorization of various types of anaemias, therefore guaranteeing appropriate therapy and improved health results for people living at high altitudes.

REFERENCES

- WHO. The Global Prevalence of Anaemia in 2011; World Health Organization: Geneva, Switzerland, 2011.
- 2. Fisher, A.L.; Nemeth, E. Iron homeostasis during pregnancy. Am. J. Clin. Nutr.2017, 106, 1567S–1574S.
- Chaparro, C.M.; Suchdev, P.S. Anemia epidemiology, pathophysiology, and etiology in low- and middleincome countries. Ann. N. Y. Acad. Sci. 2019, 1450, 15–31. [CrossRef] [PubMed]

- WHO. Essential Nutrition Actions: Improving Maternal, Newborn, Infant and Young Child Health and Nutrition;WHO: Geneva, Switzerland, 2013.
- 5. WHO. Guideline: Intermittent Iron and Folic Acid Supplementation in Menstruating Women; WHO: Geneva, Switzerland, 2011.
- WHO. Recommendations on Antenatal Care for a Positive Pregnancy Experience; WHO: Geneva, Switzerland, 2016.
- Karakochuk, C.D.; Hess, S.Y.; Moorthy, D.; Namaste, S.; Parker, M.E.; Rappaport, A.I.; Wegmuller, R.; Dary, O. Measurement and interpretation of hemoglobin concentration in clinical and field settings: A narrative review. Ann. N. Y. Acad. Sci. 2019, 1450, 126–146. [CrossRef] [PubMed]
- 8. Korolnek, T.; Hamza, I. Macrophages and iron trafficking at the birth and death of red cells. Blood 2015, 125, 2893–2897. [CrossRef]
- Muñoz, M.; Villar, I.; García-Erce, J.A. An update on iron physiology.World J. Gastroenterol. 2009, 15, 4617–4626. [CrossRef]
- Muckenthaler, M.U.; Rivella, S.; Hentze, M.W.; Galy, B. A Red Carpet for Iron Metabolism. Cell 2017, 168, 344–361. [CrossRef] [PubMed]
- Petry, N.; Olofin, I.; Hurrell, R.F.; Boy, E.; Wirth, J.P.; Moursi, M.; Donahue Angel, M.; Rohner, F. The Proportion of Anemia Associated with Iron Deficiency in Low, Medium, and High Human Development Index Countries: A Systematic Analysis of National Surveys. Nutrients 2016, 8, 693. [CrossRef]
- WHO. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity; World Health Organization: Geneva, Switzerland, 2011.
- 13. Lynch, S. The Rationale for Selecting and Standardizing Iron Status Indicators; World Health Organization: Geneva, Switzerland, 2012.
- Haase, V.H. Hypoxic regulation of erythropoiesis and iron metabolism. Am. J. Physiol. Ren. Physiol. 2010, 299, F1–F13. [CrossRef]
- Gassmann, M.; Muckenthaler, M.U. Adaptation of iron requirement to hypoxic conditions at high altitude. J. Appl. Physiol. 2015, 119, 1432–1440. [CrossRef]
- 16. Gonzales, G.F.; Rubín de Celis, V.; Begazo, J.; Del Rosario Hinojosa, M.; Yucra, S.; Zevallos-Concha, A.; Tapia, V. Correcting the cut-off point of hemoglobin at high altitude favors misclassification of anemia, erythrocytosis and excessive erythrocytosis. Am. J. Hematol. 2018, 93, E12–E16. [CrossRef]
- Robalino, X.; Balladares-Saltos, M.; Miño, P.; Guerendiain, M. Comparison of Hemoglobin Concentration Adjusted for Altitude and Serum Iron and Ferritin to Diagnose Anemia in Childhood in Highlands. Blood 2016, 128, 2459.
- Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan—A web and mobile app for systematic reviews. Syst. Rev. 2016, 5, 210. [CrossRef]
- Sharma, P.; Misra, K. High Altitude and Hypoxia. In Management of High Altitude Pathophysiology; Academic Press: Cambridge, MA, USA, 2018; pp. 3–8.
- Alkhaldy, H.Y.; Hadi, R.A.; Alghamdi, K.A.; Alqahtani, S.M.; Al Jabbar, I.S.H.; Al Ghamdi, I.S.; Bakheet, O.S.E.; Saleh, R.A.M.;Shehata, S.F.; Aziz, S. The pattern of iron deficiency with and without anemia among medical college girl students in high altitude southern Saudi Arabia. J. Fam. Med. Prim. Care 2020, 9, 5018–5025. [CrossRef]

- Silubonde, T.M.; Baumgartner, J.; Ware, L.J.; Malan, L.; Smuts, C.M.; Norris, S. Adjusting Haemoglobin Values for Altitude Maximizes Combined Sensitivity and Specificity to Detect Iron Deficiency among Women of Reproductive Age in Johannesburg, South Africa. Nutrients 2020, 12, 633. [CrossRef]
- 22. Gebreegziabher, T.; Stoecker, B.J. Iron deficiency was not the major cause of anemia in rural women of reproductive age in Sidamazone, southern Ethiopia: A cross-sectional study. PLoS ONE 2017, 12, e0184742.
- 23. 23.Moreno-Black, G.; Quinn, V.; Haas, J.; Franklin, J.; Berard, J. The distribution of haemoglobin concentration in a sample of native high-altitude women. Ann. Hum. Biol. 1984, 11, 317–325. [CrossRef]
- Burke, R.M.; Rebolledo, P.A.; de Aceituno, A.M.F.; Revollo, R.; Iñiguez, V.; Klein, M.; Drews-Botsch, C.; Leon, J.S.; Suchdev, P.S. Early deterioration of iron status among a cohort of Bolivian infants.Matern.Child Nutr.2016, 13, e12404.
- Julian CG, Moore LG. Human Genetic Adaptation to High Altitude: Evidence from the Andes. Genes [Internet]. 2019 Feb 15;10(2):150. Available from: https://www.mdpi.com/2073-4425/10/2/150
- 26. Gonzales GF, Fano D, Vasquez-Velasquez C. Diagnosis of anemia in populations at high altitudes. Rev Peru Med ExpSaludPublica. 2017;34(4):699–708. Catalan. doi:10.17843/rpmesp.2017.344.3208
- Sharma AJ, Addo OY, Mei Z, Suchdev PS. Reexamination of hemoglobin adjustments to define anemia: altitude and smoking. Ann N Y Acad Sci.2019;1450(1):190–203. doi:10.1111/nyas.14167.
- Centers for Disease Control. CDC criteria for anemia in children and childbearing-aged women. MMWR Morb Mortal Wkly Rep. 1989;38(22):400–404.
- Sullivan KM, Mei Z, Grummer-Strawn L, Parvanta I. Haemoglobin adjustments to define anemia. Trop Med Int Heal. 2008;13(10):1267–1271. doi:10.1111/j.1365-3156.2008.02143.x.
- 30. Bertholf RL. Statistical methods for establishing and validating reference intervals. Lab Med. 2006;37(5):306–310. doi:10.1309/cbmhprfnlu1xa4xv.
- 31. Chan M; World Health Organization. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Geneva: Switz World Heal Organ; 2011.
- Buttarello M. Laboratory diagnosis of anemia: are the old and new red cell parameters useful in classification and treatment, how? Int J Lab Hematol. 2016;38:123– 132. doi:10.1111/ijlh.12500
- 33. Fischer SL, Fischer SP. Mean corpuscular volume. Arch Intern Med. 1983;143(2):282 283. doi:10.1001/archinte.1983.00350020108020
- El-Hazmi MAF, Warsy AS. Normal reference values for hematological parameters, red cell indices, Hb A2 and Hb F from early childhood through adolescence in Saudis. Ann Saudi Med. 2001;21(3–4):165–169. doi:10.5144/0256 4947.2001.165.
- 35. Nordin G, Mårtensson A, Swolin B, et al. A multicentre study of reference intervals for haemoglobin, basic blood cell counts and erythrocyte indices in the adult population of the Nordic countries. Scand J Clin Lab Invest. 2004;64(4):385–398. doi:10.1080/00365510410002797
- 36. Al MLA, Denic S, Al JON, Narchi H, Souid A-K, Al-Hammadi S. Red cell parameters in infant and children

from the Arabian Peninsula. Am J Blood Res. 2015;5(2):101–107.

- Serena V, Alessandro M, Maurizio TN, et al. Baseline haematological and biochemical reference values for healthy male adults from Mali. Pan AfrMed J. 2019;32. doi:10.11604/pamj.2019.32.5.12797
- Karita E, Ketter N, Price MA, et al. CLSI-derived hematology and biochemistry reference intervals for healthy adults in eastern and Southern Africa. PLoS One. 2009;4(2):e4401. doi:10.1371/journal.pone.0004401
- Odhiambo Č, Oyaro B, Odipo R, et al. Evaluation of locally established reference intervals for hematology and biochemistry parameters in Western Kenya. PLoS One. 2015;10(4):e0123140. doi:10.1371/journal.pone.0123140.
- 40. Kant S, Kumar R, Malhotra S, Kaur R, Haldar P. Prevalence and determinants of anemia among adult males in a rural area of Haryana, India. J Epidemiol Glob Health2019;9:128-34.
- Banerjee D, Dhar M, Pathania M, Ravikant, Rathaur VK. Mortality pattern of elderly patients at a tertiary care hospital: A study from Sub-Himalayan region, Uttarakhand, India. J Fam Med Prim Care 2019;8:426-31.
- 42. Renjini B, Raj A, Krishnendu V, Rajiv M, Divyamol S, Rakesh P. High prevalence of malnutrition and anemia among elderly at old age homes in Kerala, India. J Med Allied Sci. 2019;1:1.
- Bhasin A, Rao MY. Characteristics of anemia in elderly: A hospital based study in South India. Indian J HematolBlood Transfus 2011;27:26-32.
- Kaur M, Gk K. Burden of anaemia in rural and urban Jatwomen in Haryana State, India. Mal J Nutr 2009;15:175-84.
- 45. Malhotra VM, Kabra PR, Bhayya S, Malhotra R. Prevalence and correlates of anemia among elderly population of rural Nalgonda : A cross-sectional analytic study. Public Heal Rev Int J Public Heal Res 2016;3:166-71.
- 46. Agarwalla R, Saikia A,Parashar M, Pathak R, Islam F. Assessment of prevalence of anemia in and its correlates among community-dwelling elderly of Assam, India: A cross-sectional study. Int J NutrPharmacolNeurol Dis 2016;6:23.
- 47. Gonmei Z, Dwivedi S,Toteja GS, Singh K, Vikram NK, Bansal PG. Anemia and vitamin B12 deficiency in elderly. Asian J Pharm Clin Res 2018;11:402.
- 48. Soni PN, Jawale RB, Soni SP, Pn S, Adv IJ, May M. Study of anemia in geriatric population : A hospital based study in Marathwada region, Maharashtra, India. Int J Adv Med 2016;3:197-9.
- Shrivastava SR, Hippargi SB, Ambali AP, Yelikar BR. Patterns of anemia in geriatric age Group. JKIMSU 2013;2:77-81.
- Vadakattu SS, Ponday LR, Nimmathota A, Nagalla B, Kondru DS, Undrajavarapu P, et al. Prevalence of nutritional anaemia and hyperhomocysteinemia in urban elderly. Indian J ClinBiochem 2019;34:330-5.
- Sudarshan BP, Chethan TK. A study to assess the prevalence of anemia and activities of daily living among elderly population residing in a South Indian rural community.IntJ Community Med Public Health 2016;3:437-41
- 52. Alkhaldy HY, Awan ZA, Abouzaid AA, Elbahaey HM, Al Amoudi SM, Megahed S, et al. Effect of Altitude on Hemoglobin and Red Blood Cell Indices in

Adults in Different Regions of Saudi Arabia. International Journal of General Medicine. 2022 Mar;Volume 15:3559–65.

- 53. Gassmann M, Mairbäurl H, Livshits L, Seide S, Hackbusch M, Malczyk M, et al. The increase in haemoglobin concentration with altitude varies among human populations. Annals of the New York Academy of Sciences. 2019 Jun 30;1450(1).
- 54. Silubonde TM, Baumgartner J, Ware LJ, Malan L, Smuts CM, Norris S. Adjusting Haemoglobin Values for Altitude Maximizes Combined Sensitivity and Specificity to Detect Iron Deficiency among Women of Reproductive Age in Johannesburg, South Africa. Nutrients. 2020 Feb 27;12(3):633.
- 55. Alarcón-Yaquetto DE, Figueroa-Mujica R, Valverde-Bruffau V, Vásquez-Velásquez C, Sánchez-Huamán JJ, Jimenez-Troncoso L, et al. Hematological Parameters and Iron Status in Adult Men and Women Using Altitude Adjusted and Unadjusted Hemoglobin Values for Anemia Diagnosis in Cusco, Peru (3400 MASL). Physiologia 2022 Mar 1 2(1):1–19.
- 56. Gupta A, Ramakrishnan L, Ravindra Mohan Pandey, Hem Chandra Sati, Khandelwal R, PreetikaKhenduja, et al. Risk factors of anemia amongst elderly population living at high-altitude region of India. Journal of family medicine and primary care. 2020 Jan 1;9(2):673–3.
- 57. Ocas-Córdova S, Tapia V, Gonzales GF. Hemoglobin Concentration in Children at Different Altitudes in Peru: Proposal for [Hb] Correction for Altitude to Diagnose Anemia and Polycythemia. High Altitude Medicine & Biology. 2018 Dec 1;19(4):398–403.
- 58. Nandadeva TDP, Dissanayake A, Wijayaratne LA, Punchihewa GL, Gunawardena N. Effect of iron supplementation during high altitude training on haemoglobin and iron status of Sri Lankan middle-and long-distance athletes. Sri Lanka Journal of Medicine. 2019. Available from: https://account.sljm.sljol.info
- Kapil R. Appropriateness of Hemoglobin Cut Off's for Defining Anemia. Indian Journal of Community Health. 2017. Available from: https://iapsmupuk.org/journal/index.php/IJCH/article/v iew/756
- 60. Accinelli RA, Leon-Abarca JA. Age and altitude of residence determine anemia prevalence in Peruvian 6 to 35 months old children. PLoS One. 2020;15(8) Available from: https://journals.plos.org/plosone/article?id=10.1371/jou rnal.pone.0236431
- 61. Ahmad Y, Sharma NK, Garg I, Ahmad MF, Sharma M, Garg N, et al. An insight into the changes in human plasma proteome on adaptation to hypobaric hypoxia.PLoS One. 2013;8(1) Available from: https://journals.plos.org/plosone/article?id=10.1371/jou rnal.pone.0067548
- 62. Barrera-Reyes PK, Tejero ME, Rojas J, Moreno-Macias H, Escobar-Gutierrez A, Mejia-Arangure JM, et al. Genetic variation influencing hemoglobin levels and risk for anemia across populations. Ann N YAcad Sci. 2019;1450(1):218-231. Available from: https://nyaspubs.onlinelibrary.wiley.com/doi/full/10.11 11/nyas.14134
- 63. Al-Sweedan SA, Alhaj M, Bataineh ZA, Samara OA. The effect of low altitude on blood count parameters.HematolOncol Stem Cell Ther. 2012;5(3):158-161. Available from:

https://www.sciencedirect.com/science/article/pii/S165 8387612000576

- Stobdan T, Karar J, Pasha MAQ. High altitude adaptation: genetic perspectives. High Alt Med Biol. 2008;9(2):140-147. Available from: https://www.liebertpub.com/doi/10.1089/ham.2008.10 03
- 65. Sangeetha T, Nargis Begum T, Hamsaveni R, Srinivas G. Influence of SERPINA1 Gene Polymorphisms on Anemia and Chronic Obstructive Pulmonary Disease. J ReninAngiotensin Aldosterone Syst. 2022;23(1):14703203221079165. Available from: https://journals.sagepub.com/doi/full/10.1177/1470320 3221079165
- 66. Kotwal J, Apte CV, Kotwal A, Kamath A, Dutta V, Taksande B, et al. High altitude: a hypercoagulable state: results of a prospective cohort study. Thromb Res. 2007;120(3):391-397.