ANDES PEDIATRICA
REVISTA CHILENA DE PEDIATRÍA

www.scielo.cl

Andes pediatr. 2023;94(6):705-712
DOI: 10.32641/andespediatr.v94i6.4486

ORIGINAL ARTICLE

Correlation between serum ferritin, erythrocyte and hemoglobin indices in infants living at 3400 m altitude

Correlación entre ferritina sérica, índices eritrocitarios y hemoglobina en lactantes que viven a 3400 m de altitud

Wilfredo Villamonte-Calanche[a,b], David Orccosupa-Quispe[b], Fiorella Mendoza-Cabrera[b], Erick Flores-Gonzales[b,c], Lynda Cari-Avalos[b], Ronny Breibat-Timpo[b,d,e]

[a]Centro de Investigación de Medicina Materno Perinatal, Instituto de Investigación de la Universidad Andina del Cusco. Cusco, Perú.
[b]Asociación Científica de Estudiantes de Medicina Humana (ACIEMH-Andina), Universidad Andina del Cusco. Cusco, Perú
[c]Estudiante de Medicina, Escuela Profesional de Medicina Humana, Universidad Andina del Cusco. Cusco, Perú
[d]Departamento de Pediatría, Hospital Nacional Adolfo Guevara Velasco de ESSALUD de Cusco. Cusco, Perú
[e]Departamento de Medicina Humana, Facultad de Medicina Humana, Universidad San Antonio Abad del Cusco. Cusco, Perú

Received: August 2, 2022; Approved: August 17, 2023

What do we know about the subject matter of this study?

In Peru, the prevalence of anemia is a public health problem. About 50% of newborns suffer from this condition, with iron deficiency as the main cause. The World Health Organization recommends hemoglobin measurement for its diagnosis. About 11 million Peruvians live in high-altitude cities, where a correction factor is used to correct the hemoglobin value obtained, thus increasing the diagnostic thresholds and prevalence of anemia. The use of this hemoglobin correction factor according to altitude for the diagnosis of anemia is debatable.

What does this study contribute to what is already known?

In this study, we show that the erythrocyte indexes, mean corpuscular volume, and mean corpuscular hemoglobin have the best correlation with serum ferritin levels compared with hemoglobin. Besides, the cut-off point Hb 12.15 g/dL best predicts iron deficiency in 6-month-old newborns living at 3400 m.a.s.l.

Abstract

Anemia (An) is a public health problem in South America, with iron deficiency (ID) as the main cause. In high-altitude cities, hypobaric hypoxia causes an increase in hemoglobin (Hb) levels in residents. For the diagnosis of An, Hb is measured, which is modified after erythrocyte indices (EI) measurements. There is evidence that there is an overestimation of the prevalence of An at high altitudes. **Objective:** To correlate serum ferritin (SF) with Hb and EI, and to determine the Hb cut-off point for predicting ID in 6-month-old infants at 3400 m of altitude. **Subjects and Method:** 128 infants

Keywords:
Ferritin;
Erythrocyte Indices;
Infant;
Altitude;
Hypoxia

Correspondence:
David Orccosupa Quispe
bresukite@gmail.com

Edited by:
Macarena Lizama Calvo

How to cite this article: Andes pediatr. 2023;94(6):705-712. DOI: 10.32641/andespediatr.v94i6.4486

aged 6 months at 3400 m altitude were evaluated. The SF was considered an independent variable. IE and Hb were the dependent variables. The An in the infant was defined with an Hb < 13.4 g/dl. The DH was defined by FS <12 ug/dL. Data were processed in SPSS® version 25. Spearman correlation was used for bivariate analysis. The ROC curve was constructed to determine the Hb cut-off point for ID. **Results:** The highest correlation of SF was observed with mean corpuscular hemoglobin (MCH), rho = 0.449 ($p < 0.001$), and mean corpuscular volume (MCV) rho= 0.423 ($p < 0.001$). The Hb cut-off point according to SF, defining ID was 12.15 g/dL (ROC curve: 0.704; 95% CI: 0.597-0.811; $p < 0.001$). **Conclusion:** MCV and MCH showed a better correlation with SF. The cubic and logarithmic models were the ones that best represented these relationships, respectively. Hb < 12.15 g/dL allows diagnosing ID in 6-month-old infants at 3400 m altitude.

Introduction

In 1968, the World Health Organization (WHO) defined anemia as hemoglobin (Hb) levels < 11 g/dL in newborns ≥ 6 months of age at < 1000 m.a.s.l.[1,2]. anemia is a public health problem in Asia, Africa, and South America[3], and its prevalence in Peruvian children is 43.6%[4]. Its main cause is iron deficiency (ID)[5,6], which generates cognitive deficiencies and behavioral alterations in children[7]. In Peru, the prevalence of anemia has not changed in the last decade, despite the various iron (Fe) supplementation strategies implemented[8].

Hb is a molecule composed of 4 globin chains (2 alpha and 2 beta) attached to the heme group[9]. It transports oxygen and carbon dioxide; the heme group binds oxygen through iron (oxyhemoglobin) and is carried from the lungs to the tissues. At this level, it binds to carbon dioxide to return to the lungs where it is released, favoring oxygen binding.

Ferritin is a protein responsible for storing Fe in the human body and is found in the cytosol and blood. Serum ferritin (SF) is an indirect marker of the total amount of iron stored[10]. SF concentrations < 12 ug/dL allow the diagnosis of ID[8,11], with 82% sensitivity and 95% specificity[12]. Inflammatory processes may affect its levels, so it is appropriate to measure acute phase reactants such as C-reactive protein (CRP) or hepcidin simultaneously, in order to rule out these processes[13,14].

Hypobaric hypoxia (HH) is a condition in high-altitude cities that generates an increase in the number of erythrocytes and Hb levels in people who live there in response to the increase of erythropoietin[15,16]. In adapted populations (people who have experienced changes by epigenetic processes over time in response to HH)[17] this is not evident[18]. For this reason, the WHO recommends using Hb levels with an altitude correction factor (ACF), which was determined through the formula proposed by the Centers for Disease Control and Prevention (CDC)[19]. The ACF should be added to the 11 g/dL which is the threshold for anemia at sea level. For a population living at 3400 m.a.s.l., the recommended Hb ACF is 2.4 g/dL, consequently, for 6 months of age, the cut-off point established to define anemia is <13.4 g/dL[8]. There is controversy regarding this cut-off point, because Hb levels present physiological variations during the first three years of life[20], and there is no clinical evidence to support it[21], which would generate an overdiagnosis of anemia.

Erythrocyte indexes (EI) include mean corpuscular volume (MCV), which is the mean size of each erythrocyte; mean corpuscular Hb concentration (MCHC), which is the amount of Hb in a given volume of red blood cells; mean corpuscular Hb (MCH), which is the mean amount of Hb contained in each red blood cell. The decrease in each of them is related to decreased levels of SF[22,23]. Finally, the red cell distribution width (RDW) measures the variability of red blood cell size. There is no information on the correlation between SF and EI in newborns from high-altitude cities, but there is a 21% positive correlation with MCHC and a 25% negative correlation with RDW in pregnant women from high-altitude cities[24]. The main objective of this study was to establish the correlation between SF and EI, as well as with Hb. Secondarily, the Hb cut-off point for SF defining ID in 6-month-old newborns living at 3400 m.a.s.l. was determined.

Subjects and Method

Study design and population

Analytical cross-sectional study conducted from June 2021 to February 2022 in the primary healthcare centers (PHC) "*Centro Médico Metropolitano*", "*Policlínico San Sebastián*", and "*Centro Médico Santiago*" of the *Red Asistencial del Seguro Social de Salud* (EsSalud), in Cusco at 3400 m.a.s.l. and included 128 newborns aged 6 months. The sample was calculated using the EPIDAT 4.2 statistical software (developed by the Consellería de Sanidade, Xunta de Galicia, Spain; Pan American Health Organization, and CES University of

Colombia). For this purpose, the information published by McCarthy et al.[25] was used, with a 95% confidence interval and 80% power, which finally resulted in a sample size of 123 newborns.

Participants

The study included newborns seen at the EsSalud PHCs, whose parents had agreed to participate in the study and met the inclusion criteria (newborns without pathology or anomalies, from single pregnancy, born at term at 3400 m.a.s.l.). Those newborns with a history of perinatal asphyxia or Apgar score < 7 points at 5 minutes, children with congenital malformations, clinically ill, birth weight < 2500 g, and with a CRP level > 5 mg/dL were excluded.

Variables

SF was considered an independent variable and EI and Hb levels were the dependent variables. Anemia was established when the newborn's Hb levels were < 3.4 g/dL[26]. ID was defined by SF < 12 ug/dL[2].

Procedure

Selected newborns underwent a 4 mL venous puncture blood collection. To evaluate SF, 3 mL of blood was collected in a sodium citrate tube and processed in the AIA-900 Analyzer (Tosoh Bioscience Inc., USA). To determine Hb and EI, 1 mL of blood was collected in an EDTA anticoagulant tube and processed in the BC-5300 analyzer (Mindray, China). Sample processing was performed within 2 hours of sample collection. The rest of the descriptive variables of the child (sex, current weight, gestational age at birth, delivery route, birth weight, and length) were obtained from the newborn's clinical history. All the information was recorded on a data collection form.

Data processing

The IBM® SPSS® version 25 statistical software was used for data analysis. The normality of the data was determined using the Kolmogorov-Smirnov test, using mean and standard deviation (SD) for the variables with a normal distribution (weight and current Hb in addition to weight, length, and gestational age at birth), as well as median and interquartile ranges (IQR) for those with a non-normal distribution (newborn age, MCV, MCHC, MCH, RDW, and SF). For this reason, Spearman's correlation was used, considering a $p < 0.05$ value statistically significant, to see the relationship of the variables and then the best mathematical model for the best data distribution function was determined. Using the statistical software G*Power 3.1, the effect size was obtained through the chi-square test, as well as the statistical power. The Receiver Operating Characteristic (ROC) curve was elaborated and the Hb cut-off point for SF defining ID was established through the highest Youden index.

Ethical considerations

The study protocol was evaluated and approved by the Ethics Committee of the *Red Asistencial EsSalud Cusco* (Note No 34-CE-GRACU-ESSALUD-2021) and endorsed by management resolution N°364-GRACU-ESSALUD-2021. Informed consent was obtained from the parents of the newborn studied. The information on each case was handled anonymously.

Results

From a total of 1,453 births registered from January to August 2021 in the EsSalud Healthcare Network of Cusco, 176 children were selected according to the inclusion criteria and only 138 parents agreed to participate by signing the corresponding authorizations. Finally, the study was carried out with 128 participants (Figure 1).

The median age of the newborns was 199 days (IQR:191 - 205.5), male sex was predominant (53.9%), the mean weight on the day of evaluation was 8024.8 g, and 52% of the newborns studied were born via cesarean section. 28.1% had ID and the prevalence of anemia was 69.5% (Table 1).

The median Hb observed was 12.76 g/dL (SD: 1.1). The median MCH was 26.5 pg/dL (IQR: 25.3 - 27.2), and SF was 56.5 ng/mL (IQR: 27.5 - 86.5) (Table 2). The correlation of SF with MCH and MCV was moderate positive with rho = 0.449 ($p < 0.001$) and rho = 0.423 ($p < 0.001$), respectively. With Hb, it was weak positive rho = 0.299 ($p = 0.001$). In all cases, the effect size was large and the statistical power was higher than 80% (Table 3), and the best fitting models were the logarithmic and cubic ones, respectively (Graph 1).

The cut-off point of Hb for SF defining ID was 12.15 g/dL, with an ROC curve: 0.704 (95%CI: 0.597 - 0.811; $p < 0.001$), 87% sensitivity, and 47.2% specificity (Graph 2).

Discussion

In 6-month-old newborns living at 3400 m.a.s.l., there was a better correlation between SF and MCH, as well as MCV, compared with Hb. Similarly, the Hb threshold (12.15 g/dL) was determined to diagnose ID in this population.

The correlation between MCV and MCH as well as the cubic and logarithmic model relating these to SF, in 6-month-old newborns living at 3400 m.a.s.l., are explained by a decrease in the production of globin chains in the red blood cell due to ID, so there is a lower synthesis of Hb and, consequently, a lower cell volume[24], therefore, MCH is an early and more sensitive indicator of ID[23]. In the initial phase of anemia due to ID, erythrocytes are of different sizes, between normal and small, consequently, RDW increases[27] and explains the negative correlation observed in our study. Besides, McCarthy et al.[25] found a lower correlation using Pearson's test between SF and MCV ($r = 0.282$; $p < 0.001$) in 2-year-old children living at sea level, which could be explained by a higher frequency of inflammatory pathology in this population, which were not excluded in this study and which would have conditioned a higher ID and increased SF[20].

A weak positive correlation was determined and the model that generated the best coefficient of determination ($R2 = 0.168$) was the logarithmic model between SF and Hb. These findings are similar to those found by Ahmad et al. [28] ($rho = 0.170$; $p = 0.003$) in a population with a mean age of 67 months, but different from those determined by Kusumastuti et al.[29] ($rho = -0.222$; $p = 0.043$) who also did not discriminate newborn population (6-59 months) with an inflammatory process that could increase SF. The observed weak correlation could be due to a lower frequency of anemia (4.7%) in the study population if we did not

Table 1. Characteristics of the study population

Sex	n (%)
Male	
Female	69 (53.9)
Type of delivery	59 (46.1)
Vaginal	
Caesarean section	61 (47.7)
Iron status	67 (52.3)
No iron deficiency	
Iron deficiency	92 (71.9)
Con deficiencia de hierro	36 (28.1)
Anemia prevalence	89 (69.5)
Age (days)	199 (191-205.5)
Observed weight (g)	8.024.8 (781.3)
Birth weight (g)	3.246.2 (363.3)
Length at birth (cm)	49.3 (1.6)
Gestational age at birth (weeks)	39 (38-40)

Table 2. Ferritin, hemoglobin and erythrocyte indices.

Variable	Mean (SD)
Hemoglobin (g/dl)	12.7 (1.1)
	Mediana (RIC)
Mean corpuscular volume (fl)	77.2 (74.6 - 78.9)
Mean corpuscular hemoglobin concentration (g/dl)	34.2 (33.3 - 34.9)
Mean corpuscular hemoglobin (pg)	26.5 (25.3 - 27.3)
Red cell distribution width (%)	12.3 (11.9 - 13.1)
Serum ferritin (ng/ml)	56.5 (27.5 - 86.5)
Amplitud de eritrocitos (%)	12.3 (11.9 - 13.1)

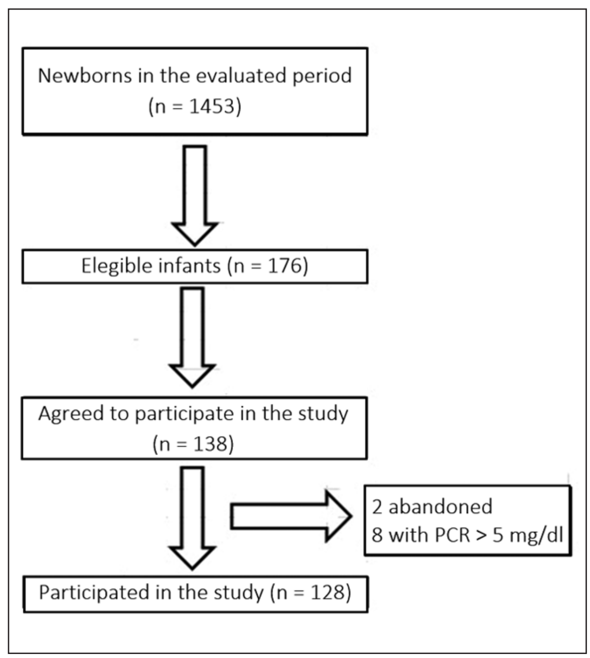
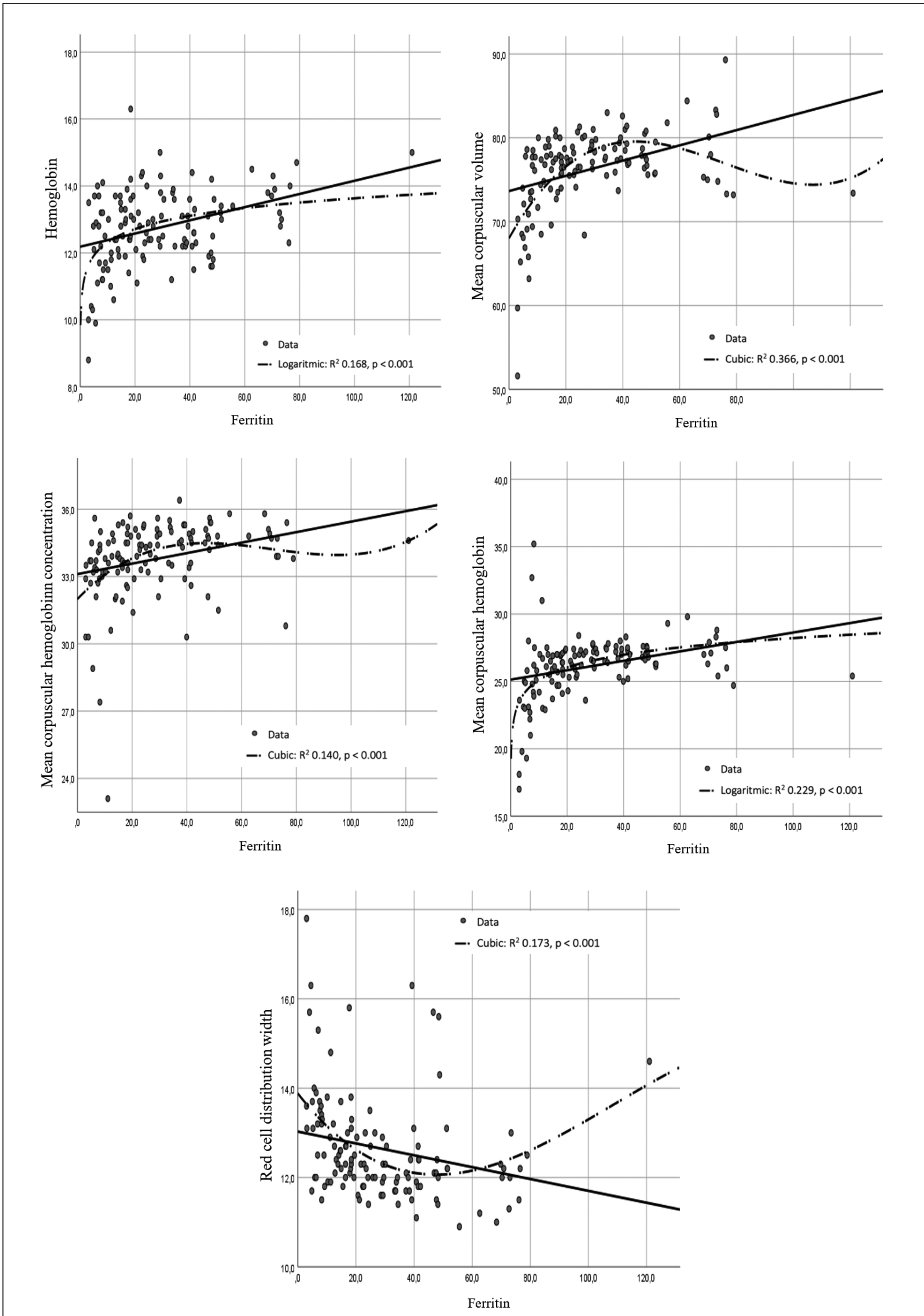


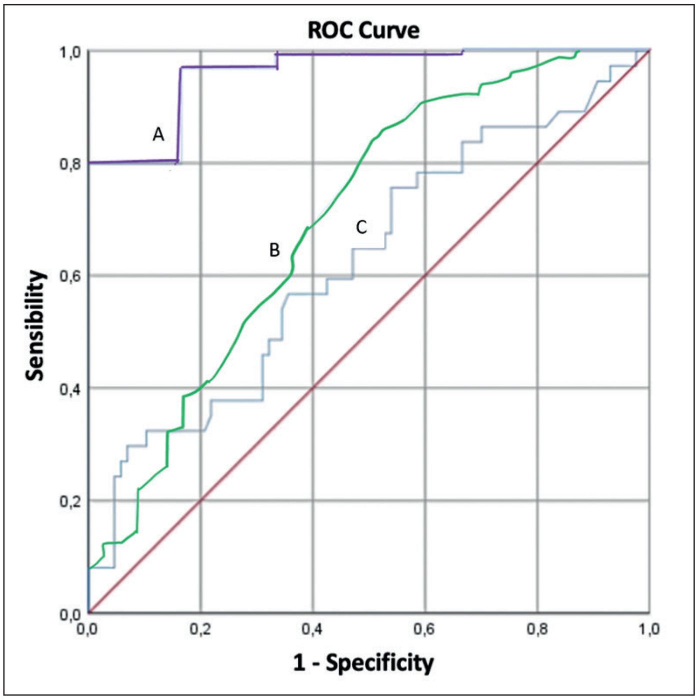
Figure 1. Participant inclusion flowchart

Table 3. Correlation of hemoglobin and erythrocyte indices with serum ferritin (n = 128)

Spearman's rank correlation coefficient (rho)				
Serum ferritin (ng/ml)	Rho coefficient	p-value	Effect size	Statistical power
Hemoglobin (g/dl)	0.299	< 0.001	0.547	0.999
Mean corpuscular volume (fl)	0.423	< 0.001	0.650	1
Mean corpuscular hemoglobin concentration (g/dl)	0.397	< 0.001	0.630	1
Mean corpuscular hemoglobin (pg)	0.449	< 0.001	0.670	1
Red cell distribution width (%)	-0.373	< 0.001	0.611	1



Graph 1. Scatter plots of hemoglobin and erythrocyte indices with serum ferritin.



Graph 2. ROC curve for determining the hemoglobin cut-off level to identify the serum ferritin level.**A:** Hb of 11 g/dl that identified a serum ferritin of 5.7 ug/dl (0.958(0.896-1)). **B:** Hb of 12.15 g/dl that identified a serum ferritin of 12 ug/dl (0.704(0.597-0.811)). **C:** Hb of 13.4 g/dl that identified a serum ferritin of 48.65 ug/dl (0.634(0.514-0.735)).

use the ACF. Likewise, ID is a condition that could exist in a child before Hb levels are affected since this is a late marker of this pathology[14,23].

The frequency of anemia was 69.5% and ID was 28.1% in the newborns evaluated, which is not consistent, especially when iron deficiency conditions are the main cause of anemia[3]. For this reason, it would seem that the use of ACF in newborns living at 3400 m.a.s.l. would not show a real prevalence of anemia due to ID[20,30], as reported by the Peruvian Ministry of Health, where the frequency of anemia (using ACF) in children aged 6 to 35 months is 43.6%, being higher in departments located above 3000 m.a.s.l., such as Puno (75.9%) and Cusco (56.6%), among others[4]. Therefore, it would be advisable to establish cut-off points for Hb for each population, since it does not have the same behavior at different ages, altitude levels, and pregnancy, among other factors[30]. In addition, how the ACF was obtained comes from a mathematical model[21,31].

The cut-off point Hb 12.15 g/dL to determine ID in 6-month-old newborns living at 3400 m.a.s.l., despite a weak correlation between the two (sensitivity 87% and specificity 47.2%), would allow better prescribing of Fe treatment and avoid its adverse effects when administered to children without ID, such as decreased weight gain and linear growth[5,32], decreased absorption of other trace elements[33], increase and duration of diarrheal diseases[34], and alteration of the microbiota[35] and cognitive development[36], among others. Also, Hb levels of 13.4 g/dL (threshold for the diagnosis of anemia in a population living at 3400 m.a.s.l.)[8] corresponds, according to the ROC curve determined, to an SF level of 48.65 ug/dL, which shows that many children with this value or less do not have ID and do not need treatment with Fe. In contrast, an Hb level of 11 g/dL (threshold for anemia at sea level) is associated with an SF of 5.7 ug/dL.

On the one hand, the strength of our study is that it was conducted in a socioeconomically intermediate and homogeneous population living at 3400 m.a.s.l. but, on the other hand, a limitation was not having determined IL-6, IL-8, and hepcidin levels, which would have allowed us to better evaluate the inflammatory picture in newborns, as well as not having information on maternal Hb levels at the end of gestation, and time of umbilical cord clamping at birth, among other factors.

We concluded that MCV and MCH presented the best correlation with SF and that the cubic and logarithmic models are the ones that best represented these relationships, respectively. A Hb level < 12.15 g/dL allows the diagnosis of ID in 6-month-old newborns living at 3400 m.a.s.l.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Universidad Andina del Cusco, Dirección de Gestión

de la Investigación y Producción Intelectual. Resolution No 041-CU-2020-UAC.

Acknowledgments

Thanks to M.C. Wilber Silva Cáceres, M.C. Martin Hilares Luna, M.C. Jorge Alberto Soto La Serna Peralta, M.C. Charles Augusto Huamani Saldaña, Lic. Zaida Quispe Merma, Lic. Lily Aslla Sullca, Lic. Angelica Marroquin Urquizo, Lic. Mery Peña Flores, Lic. Alejandrina Mora Quispe, Lic. Maritza Umeres Florez, and Lic. Dannia Gutierrez Zevallos for their support and facilitate data collection.

References

1. World Health Organization. El Uso clínico de la sangre en medicina, obstetricia, pediatría y neonatología, cirugía y anestesia, trauma y quemaduras [Internet]. Organización Mundial de la Salud; 2002 [citado 11 de octubre de 2022]. Disponible en: https://apps.who.int/iris/handle/10665/42431.
2. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser. 1968;405:5-37.
3. Allali S, Brousse V, Sacri AS, Chalumeau M, de Montalembert M. Anemia in children: prevalence, causes, diagnostic work-up, and long-term consequences. Expert Rev Hematol. 2017;10(11):1023-8. doi: 10.1080/17474086.2017.1354696.
4. Ministerio de Salud del Perú. Documento Técnico: Plan Nacional para la reducción y control de la Anemia materno infantil y la desnutrición crónica infantil en el Perú. 2017-202. 1ª ed; 2017.
5. Pasricha SR, Tye-Din J, Muckenthaler MU, Swinkels DW. Iron deficiency. Lancet. 2021;397(10270):233-48. doi: 10.1016/S0140-6736(20)32594-0.
6. Mattiello V, Schmugge M, Hengartner H, von der Weid N, Renella R; SPOG Pediatric Hematology Working Group. Diagnosis and management of iron deficiency in children with or without anemia: consensus recommendations of the SPOG Pediatric Hematology Working Group. Eur J Pediatr. 2020;179(4):527-545. doi: 10.1007/s00431-020-03597-5.
7. McCann JC, Ames BN. An overview of evidence for a causal relation between iron deficiency during development and deficits in cognitive or behavioral function. Am J Clin Nutr. 2007;85(4):931-45. doi: 10.1093/ajcn/85.4.931.
8. Ministerio de Salud del Perú. Norma técnica-Manejo terapéutico y preventivo de la anemia en niños, adolescentes, mujeres gestantes y puérperas [Internet]. 2017. Disponible en: https://www.gob.pe/institucion/minsa/informes-publicaciones/280854-norma-tecnica-manejo-terapeutico-y-preventivo-de-la-anemia-en-ninos-adolescentes-mujeres-gestantes-y-puerperas.
9. Ahmed MH, Ghatge MS, Safo MK. Hemoglobin: Structure, Function and Allostery. Subcell Biochem. 2020;94:345-82. doi: 10.1007/978-3-030-41769-7_14.
10. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: Past, present and future. Biochim Biophys Acta. 2010;1800(8):760-9. doi: 10.1016/j.bbagen.2010.03.011.
11. World Health Organization. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations [Internet]. Geneva: World Health Organization; 2020 [citado 2 de julio de 2022]. Disponible en: https://apps.who.int/iris/handle/10665/331505.
12. World Health Organization/Centers for Disease Control and Prevention Technical Consultation on the Assessment of Iron Status at the Population Level (2004: Geneva S. Assessing the iron status of populations: including literature reviews: report of a Joint World Health Organization/Centers for Disease Control and Prevention Technical Consultation on the Assessment of Iron Status at the Population Level, Geneva, Switzerland, 6-8 April 2004 [Internet]. 2nd ed. Geneva: World Health Organization; 2007 [citado 2 de julio de 2022]. Disponible en: https://apps.who.int/iris/handle/10665/75368.
13. Burke RM, Rebolledo PA, Fabiszewski de Aceituno AM, et al. Early deterioration of iron status among a cohort of Bolivian infants. Matern Child Nutr. 2017;13(4):e12404. doi: 10.1111/mcn.12404.
14. Baker RD, Greer FR; Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics. 2010;126(5):1040-50. doi: 10.1542/peds.2010-2576.
15. Muckenthaler MU, Mairbäurl H, Gassmann M. Iron metabolism in high-altitude residents. J Appl Physiol (1985). 2020;129(4):920-5. doi: 10.1152/japplphysiol.00019.2020 . 2020;129(4):920-5.
16. Trompetero-González AC, Cristancho E, Benavides W, Soto E, Caballero D. Efectos de la exposición a la altura sobre los indicadores de la eritropoyesis y el metabolismo del hierro. Rev Fac Med. 2015;63:717-25.
17. Julian CG. Epigenomics and human adaptation to high altitude. J Appl Physiol (1985). 2017;123(5):1362-70. doi: 10.1152/japplphysiol.00351.2017
18. Simonson TS, Wei G, Wagner HE, et al. Low haemoglobin concentration in Tibetan males is associated with greater high-altitude exercise capacity. J Physiol. 2015;593(14):3207-18. doi: 10.1113/JP27051.
19. Centers for Disease Control (CDC). CDC criteria for anemia in children and childbearing-aged women. MMWR Morb Mortal Wkly Rep. 1989;38(22):400-4.
20. Gonzales GF, Fano D, Vásquez-Velásquez C. Necesidades de investigación para el diagnóstico de anemia en poblaciones de altura. Rev Peru Med Exp Salud Publica. 2017;34(4):699-708.
21. Villamonte-Calanche W, Lam-Figueroa N, Jerí-Palomino M, De-La-Torre C, Villamonte-Jerí AA. Maternal Altitude-Corrected Hemoglobin and at Term Neonatal Anthropometry at 3400 m of Altitude. High Alt Med Biol. 2020;21(3):287-91. doi: 10.1089/ham.2019.0127.
22. Campuzano Maya G. Interpretación del hemograma automatizado: claves para una mejor utilización de la prueba. Med Lab. 2013;11-68.
23. Archer NM, Brugnara C. Diagnosis of iron-deficient states. Crit Rev Clin Lab Sci. 2015;52(5):256-72. doi: 10.3109/10408363.2015.1038744.
24. Han AP, Yu C, Lu L, et al. Heme-regulated eIF2alpha kinase (HRI) is required for translational regulation and survival of erythroid precursors in iron deficiency. EMBO J. 2001 Dec 3;20(23):6909-18. doi: 10.1093/emboj/20.23.6909
25. McCarthy EK, Ní Chaoimh C, Kenny LC, et al. Iron status, body size, and growth in the first 2 years of life. Matern Child Nutr. 2018;14(1):e12458. doi: 10.1111/mcn.12458
26. Imeri F, Herklotz R, Risch L, et al. Stability of hematological analytes depends on the hematology analyser used: a stability study with Bayer Advia 120, Beckman Coulter LH 750 and

Sysmex XE 2100. Clin Chim Acta. 2008;397(1-2):68-71. doi: 10.1016/j.cca.2008.07.018.
27. Dugdale AE. Predicting iron and folate deficiency anaemias from standard blood testing: the mechanism and implications for clinical medicine and public health in developing countries. Theor Biol Med Model. 2006;3:34. doi: 10.1186/1742-4682-3-34.
28. Ahmad MS, Fatima R, Farooq H, Maham SN. Hemoglobin, Ferritin levels and RBC Indices among children entering school and study of their correlation with one another. J Pak Med Assoc. 2020;70(9):1582-6. doi: 10.5455/JPMA.15046.
29. Tri Kusumastuti F, Sutaryo S, Mulatsih S. Correlations between hemoglobin, serum ferritin, and soluble transferrin receptor levels in children aged 6-59 months. PI [Internet]. 30Apr.2014 [cited 5 Sep. 2023];54(2):122.
30. Accinelli RA, Leon-Abarca JA. Age and altitude of residence determine anemia prevalence in Peruvian 6 to 35 months old children. PLoS One. 2020 Jan 15;15(1):e0226846. doi: 10.1371/journal.pone.0226846
31. WHO | Assessing the iron status of populations [Internet]. WHO. World Health Organization; 2007 [citado 5 de octubre de 2020]. Disponible en: http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/9789241596107/en/
32. Dewey KG, Domellöf M, Cohen RJ, Landa Rivera L, Hernell O, Lönnerdal B. Iron supplementation affects growth and morbidity of breast-fed infants: results of a randomized trial in Sweden and Honduras. J Nutr. 2002;132(11):3249-55. doi: 10.1093/jn/132.11.3249.
33. Domellöf M, Dewey KG, Cohen RJ, Lönnerdal B, Hernell O. Iron supplements reduce erythrocyte copper-zinc superoxide dismutase activity in term, breastfed infants. Acta Paediatr. 2005;94(11):1578-82. doi: 10.1080/08035250500252674.
34. Soofi S, Cousens S, Iqbal SP, et al. Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial. Lancet. 2013;382(9886):29-40. doi: 10.1016/S0140-6736(13)60437-7.
35. Paganini D, Zimmermann MB. The effects of iron fortification and supplementation on the gut microbiome and diarrhea in infants and children: a review. Am J Clin Nutr. 2017 Dec;106(Suppl 6):1688S-1693S. doi: 10.3945/ajcn.117.156067.
36. Lönnerdal B. Excess iron intake as a factor in growth, infections, and development of infants and young children. Am J Clin Nutr. 2017;106(Suppl 6):1681S-1687S. doi: 10.3945/ajcn.117.156042.