LITERATURE REVIEW
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Biochemistry Indicators for the Identification of Iron Deficiency Anemia in Indonesia: A Literature Review

Tinjauan Literatur: Indikator Biokimia untuk Identifikasi Anemia Defisiensi Zat Besi di Indonesia

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ABSTRACT

Background: *The World Health Organization (WHO) states that adolescents are at risk of developing anemia. The initial step in identifying iron deficiency anemia (IDA) is through screening. In addition, the WHO framework aims to accelerate the reduction of anemia worldwide by achieving specific goals, including an increase in anemia screening.*
Objectives: *This study aims to determine the use of biochemical indicators in screening for the identification of IDA status in Indonesia.*
Methods: *Literature searches were conducted in the PubMed, Scopus, ScienceDirect, and Garuda databases following the PRISMA guidelines. Articles from journals indexed in Scopus Q1 to Q4 or Sinta 1 to Sinta 3 with an experimental or observational research design in Indonesia were reviewed.*
Discussion: *Anemia screening was performed to determine IDA status, which was measured by the following parameters: hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). Hb is an indicator of IDA in populations with a high prevalence of IDA. MCV is calculated by dividing hematocrit by red blood cell count. MCH refers to the average absolute hemoglobin content of the red blood cells, while MCHC refers to the concentration of hemoglobin in the red blood cells. Serum ferritin (SF) is a highly reliable and sensitive indicator for assessing iron stores and clinical status in the field. In addition, serum transferrin receptor (STfR) is a more stable indicator than serum transferrin (ST). SF can differentiate between IDA caused by anemia or chronic diseases.*
Conclusions: *Combining hemoglobin and SF improves sensitivity and specificity in detecting the severity of IDA. STfR can also be used as an indicator for IDA. The use of the STfR and SF indicators is the best biochemical approach to IDA.*

INTRODUCTION

Anemia is a common health problem in developing countries, especially in Indonesia, affecting individuals of all ages. The World Health Organization (WHO) reported that in 2014, adolescents aged 10-19 years are at risk of anemia due to their rapid growth and increased nutritional needs for physical and cognitive development. it is crucial to address this issue to ensure the well-being of the younger generation[1]. In addition, adolescent girls are not affected in terms of quality of life such as productivity, but they also indirectly affect the nutritional status of their children in the future[2].

Anemia is a condition characterized by a decrease in the amount of red blood cells or hemoglobin. Approximately 50% percent of anemia cases are due to iron deficiency[3]. Clinical symptoms of anemia include as fatigue, dizziness, dyspnea, palpitations, and pale conjunctiva and palms. Anemia is determined at a health

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center by assessing hemoglobin levels[4]. Anemia occurs when the levels of hemoglobin (Hb), hematocrit (Hct), and red blood cells per unit volume are lower than the reference blood parameters. According to the definition by the WHO, anemia can be identified by the following criteria: hemoglobin levels of less than 13 g/dL for males aged over 15 years, less than 12 g/dL for females aged over 15 years and not pregnant, and less than 11 g/dL for pregnant women[5]. In cases of iron deficiency anemia, it is important to assess ferritin levels and/or transferrin saturation values in addition to Hb. The WHO criteria for diagnoses are as follows: Hb less than 11.5 g/dL (for children aged 6-11 years); Hb less than 12 g/dL (for adolescent girls aged 12-15 years and 15-18 years if not pregnant); Hb less than 13 g/dL (for adolescent boys aged 15-18 years); and transferrin saturation of less than 15% and/or ferritin levels of less than 15 mg/L[6].

Iron deficiency is the most common cause of anemia, known as iron deficiency anemia. It happens when the body lacks enough iron to produce new red blood cells[2]. Indicators of iron deficiency anemia include hypochromic red blood cells, decreased levels of serum iron and transferrin, and increased total iron binding capacity (TIBC). In adolescents, iron deficiency anemia can cause physical and mental growth and development problems, leading to decreased fitness, work ability, and school performance[7-9]. During adolescence, factors such as increased body mass, blood volume, and red blood cell mass can reduce iron stores and increase the risk of iron deficiency. Adolescent girls have a higher prevalence of iron deficiency anemia due to blood loss during menstruation[10]. Children and adolescents from low socioeconomic backgrounds are more susceptible to iron deficiency anemia due to inadequate iron intake and low bioavailability of iron-rich foods[11].

Early detection or screening using biochemical indicators is important for the early identification of iron deficiency anemia[12]. Screening plays a crucial role in determining the prevalence of anemia in the population, allowing for prioritization of interventions such as providing blood supplement tablets to individuals with anemic conditions. This literature review aims to provide an overview of the biochemical indicators used for the identification of iron deficiency anemia in Indonesia, in line with the WHO framework to accelerate the reduction of anemia worldwide, especially through screening[13].

METHODS

This literature review was conducted using the narrative method and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The search was performed in November 2023 on using international databases, namely PubMed, Scopus, and ScienceDirect, and a national database, namely Garuda. Only articles published between 2013 to 2023 were included. The search keywords used were "Anemia AND Iron Deficiency AND prevalence AND adolescent AND Indonesia" in the international databases and "Anemia AND iron deficiency AND prevalence AND adolescent AND Indonesia" in the national database. This literature review included articles that met specific inclusion criteria. These criteria required that the articles be original, have an experimental or observational research design, be conducted with the Indonesian population, be available in Indonesian or English, be in accordance with the research objective, and be from journals indexed in Scopus Q1 to Q4 or Sinta 1 to Sinta 3, as presented in Figure 1.

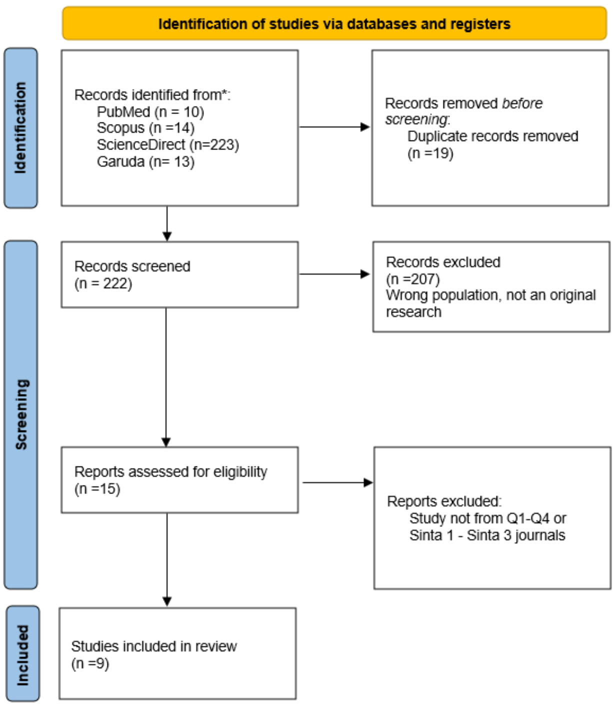

Figure 1. PRISMA flowchart of the article search

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Table 1. General characteristics of the study

No	Article title/author	Research design	Age of subject	Number of Subjects	Research location	Biochemical Indicators	Research Results
1	Prevalence of anemia and iron profile among children and adolescent with low socio-economic status	Cross-sectional	6-18 years	242	Jakarta	Hb, Hct, MCV, MCH, MCHC, Ret-He, ferritin, serum iron, and total iron-binding capacity (TIBC).	● The overall prevalence of anemia was 14%. ● The prevalence of iron deficiency anemia, iron deficiency without anemia, and iron depletion was 5.8%, 18.4% and 4.3%, respectively. ● All of these were higher in women.
2	Plant-based diet an iron deficiency anemia in Sundanese adolescent girls at Islamic boarding schools in Indonesia	Quantitative with analytical design and a cross-sectional approach	10-19 years	176	Tasikmalaya, West Java	Hb, MCV, MCH, MCHC	● The prevalence of iron deficiency anemia in this study was 22.2%. ● Iron intake was lower than the recommended amount of 6.59 mg/day. ● There was a correlation between heme iron, Hb, and Hct. Iron from meat, fish and poultry correlated with Hb and Hct levels.
3	Iron deficiency anemia and associated factors among adolescent girls and women in a rural area of Jatinangor, Indonesia	Cross-sectional	10-35 years	95 adolescent girls and 85 adult women	Jatinangor, West Java	Hb and MCV	● The prevalence of iron deficiency anemia among adolescent girls was 21.1% and 9.4% among adult women. ● The average Hb in adolescents was 10.75 g/dL and in adults was 11.3 g/dL, while the MCV in adolescents was 74.49±8.22 fL and in adults was 7.61±8.62 fL. ● Protein intake had a positive correlation with anemia.
4	Probiotics Lactobacillus reuteri DSM 17938 and Lactobacillus casei CRL 431 Modestly Increase Growth, but Not Iron and Zinc Status, among Indonesian Children Aged 1–6 Years	RCT	1-6 years	494	Jakarta	Hb, Hct, RDW, MCV, MCHC, hs-CRP, AGP, sTfR, and zinc	● Compared to the control group, the group that received *L. reuteri* showed a rapid increase in body weight, change in weight-per-age Z-score, and monthly weight and height gain. ● *L. casei* increased monthly weight gain. ● Changes in underweight, stunting, prevalence of anemia, and iron and zinc status were similar between the groups.

5	Effect of giving chicken dim sum with Moringa leaf flour	Quasi-experiment, pre and post-test with control group	Adolescent girls in junior high school	60	Sijunjung, West Sumatra	Hb	● The average Hb level was 13.93 before the intervention and 14.37 post intervention. ● The results suggested an effect of interventions on the Hb levels of adolescent girls.
6	Iron status, prevalence and risk factors of iron deficiency anemia among 12- to 15-year-old adolescent girls from different socioeconomic status in Indonesia	Cross-sectional	12-15 years	163	Central Jakarta	Serum iron, ferritin, TIBC, transferrin	● Iron status was normal in 69.3% of the 163 subjects. ● The prevalence of iron deficiency was higher (17.2%) than the prevalence IDA (13.5%). ● The prevalence of IDA was lower among girls with high economic status (11.5%) than among girls with low economic status (15.8%).
7	Cost-effectiveness of ferrous fumarate-folic acid and ferrous gluconate-multivitamins in a high prevalence area of iron deficiency anemia in Indonesia	Prospective observational	15-49 years	875	West Papua	Hb	● About 222 women had moderate iron deficiency anemia. ● There were significant differences in the number of respondents, age, oral iron cost, health cost, and utility score between the two intervention groups. ● When comparing the use of FG-MV with FF-FA, the estimated incremental cost-effectiveness (ICERs) was $255.77 per patient; $142.94 for a patient with Hb above 2.00 g/dL; $79.93 for one patient with Hb above 1.00g/dL; and $11.59/QALY.
8	Iron profile in adolescent scavengers living in slum areas	Cross-sectional	10-18 years	96	Bekasi, West Java	Hb, ferritin, transferrin	● The prevalence of anemia was 13.6%, and half of it was attributed to iron deficiency. ● The iron profile consisted of iron depletion (2.1%), iron deficiency (18.8%), and iron deficiency anemia (7.3%). ● Hb, ferritin, and transferrin saturation levels were significantly lower in females.
9	Dietary diversity and poverty as risk factors for leprosy in Indonesia: A case-control study	Case-control	18-65 years	300	Bangkalan, Madura	Serum iron, TIBC, ferritin, transferrin	● Irregular income, anemia, and high level of food insecurity were significantly associated with an increased risk of leprosy. ● High levels of knowledge and land ownership were found to be protective against leprosy.

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- Lack of dietary diversity and food availability, low serum iron, and high ferritin were common individuals with leprosy, but the incidence of leprosy was not significantly associated with iron deficiency.

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DISCUSSION

Table 1 lists nine articles on biochemical indicators used to identify iron deficiency anemia in Indonesia. The articles used biochemical indicators such as Hb, Hct, MCV, MCH, MCHC, Ret-He, ferritin, serum iron, and TIBC to identify iron deficiency anemia in various regions of Indonesia, including Jakarta[1,14,15], West Java[3,11,16], West Papua[17], West Sumatra[18], and Madura[19].

The World Health Organization (WHO) aims to reduce the prevalence of anemia in women of reproductive age by 50% by 2025 because anemia remains a significant health concern. One approach is to screen women of reproductive age to optimize the synthesis of hemoglobin, to prevent the excessive destruction of red blood cells, and to reduce blood loss[13]. Numerous studies have assessed the clinical impact of screening for iron deficiency anemia (IDA). Andriastuti et al. (2020) found that iron deficiency anemia identified in their study was a minor public health concern according to the classification by the WHO. Based on hemoglobin levels, anemia is classified as moderate in adolescents and mild in adults. Their study used a complete blood test to screen for anemia, measuring Hb reticulocytes, ferritin, transferrin saturation, and C-reactive protein to assess iron status. The difference in mean hemoglobin levels between adults and adolescents was due to the higher iron requirements of adolescents during growth and sufficient level of education. Mean corpuscular hemoglobin (MCH) refers to the absolute hemoglobin content of an average red blood cell, usually measured in picograms and calculated as the ratio of hemoglobin to the number of red blood cells. Low MCH levels indicate iron deficiency anemia. A study showed that iron deficiency anemia is the leading cause of anemia, accounting for approximately 60% of all causes. Other causes of anemia include thalassemia (5.40%), malaria (4.17%), ulcer and duodenitis (3.27%), and other neglected tropical diseases (3.09%)[14].

Rahfiludin et al. (2021) in their research reported that the prevalence of anemia was slightly higher than the national average, with rates of 32.0% in young adults aged 15-24 years and 26.8% in children aged 5-14 years. According to the WHO guidelines, the prevalence of anemia between 20.0% and 39.9% is classified as moderate, indicating that anemia is a public health concern for adolescent girls in the region. Of all anemic subjects, 22.2% had IDA. Anemia screening in their study used venous blood samples (3 ml) and were analyzed using the Sysmex-XNL hematology analyzer[11]. IDA status was determined using parameters such as Hb, MCV, MCH, and MCHC. The decrease in MCV due to severe iron deficiency was calculated by dividing hematocrit by red blood cell count. MCH is the absolute hemoglobin content of the average red blood cell, usually measured in picograms and calculated as the ratio of hemoglobin to the number of red blood cells. Mean corpuscular hemoglobin concentration (MCHC) refers to the concentration of hemoglobin in the red blood cells. It is important to note that MCHC is less affected by age than other indicators and decreases during iron deficiency[20].

Puspa et al. in their study reported that the prevalence of IDA indicates a minor public health concern. The study population exhibited differences in hematological parameters including hemoglobin, MCH, MCV, and MCHC. The levels of MCV and MCH may indicate low iron levels in the body. On average, the levels of MCV, MCH, and MCHC of the respondents were below normal. The low levels of MCH in the study might be an indication of iron deficiency anemia. MCH measures the amount of hemoglobin per red blood cell, while MCV is expressed in femtoliters (10-15; fL) or cubic microns (µm3). The normal level of MCV is 87 ± 7 fL. The normal level of MCHC, which indicates the amount of hemoglobin per unit volume, is 34 ± 2 g/dL, while the normal level of MCH is 29 ± 2 picograms (pg) per cell[3]. The study found a significant correlation between protein intake and anemia (29.6%, p = 0.001, OR = 0.25 [0.11-0.58]). The study suggested that adequate protein intake might be associated with the prevalence of IDA due to its role in the formation of hemoglobin. This finding is consistent with the Basic Health Research in that Indonesian adolescents consume fewer vegetables, which are a source of protein[3].

Agustina et al. (2013) conducted a six-month intervention and found that the concentration of iron parameters such as Hb, Hct, and serum ferritin decreased, while STfR increased in all groups. However, serum zinc concentration remained constant. No changes were observed in the mean iron parameters and prevalence of anemia, iron deficiency, iron deficiency anemia, or zinc status. The decrease in iron status over a six-month period, regardless of the type of intervention, might be attributed to a deficiency in iron homeostasis, which fails to compensate for the rapid mobilization of iron from stores that is required for growth[15].

Andriastuti et al. (2023) in their study found that the increased daily iron requirement of adolescent girls due to blood loss during menstruation might be a contributing factor to the higher prevalence of IDA in female subjects. All subjects with IDA were menstruating at the time of the study. The researchers reported that the average menstrual blood loss was at 84 ml per period and the average Hb was 13.3 g/dl, estimating an additional 0.56 mg of daily iron requirement[14]. The overall iron requirement for adolescent girls increased from approximately 0.7-0.9 mg per day to 1.40-3.27 mg per day. Iron status parameters in the study showed decreased ferritin, iron deficiency, and IDA below normal. Ferritin concentration may increase during acute infection, which might be an indicator for iron status. To rationalize the ferritin level, CRP was added. Combining other iron status measurements with ferritin can more accurately identify iron deficiency. The average CHr level was 27 in iron-deficient subjects, but dropped to 22.7 pg in cases of IDA. CHr has recently been recognized as a useful screening parameter for IDA and iron deficiency because it provides an alternative measure to traditional screening methods[16].

Sumarlan et al. (2018) found that iron depletion and iron deficiency are more prevalent than IDA. If left unaddressed promptly, these conditions can easily lead to IDA. However, no clear association between IDA and its risk factors was observed, and bioavailable iron intake might be a more significant risk factor in these individuals[1]. The screening process involved a complete

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blood count of Fe, ferritin, TIBC, TS. Iron status was considered normal if serum ferritin, TS, and MCV were within the normal range.

Yasinta et al. (2021) in their study identified iron status, menstrual patterns, socioeconomic status (SES), and iron intake as risk factors for IDA. The group with low SES was more likely to have problems such as increased blood loss, more frequent menstruation (more than once a month), and longer menstrual periods. Although no significant correlation between low SES and iron deficiency was observed, this finding might explain why iron deficiency is more prevalent in low SES groups[17]. Hb levels were measured using a HemoCue portable analyzer. Anemia was classified as mild iron deficiency anemia if hemoglobin levels were between 10-10.9 g/dL (for pregnant women) and 11-11.9 g/dL (for non-pregnant women), moderate if the levels were between 7-9.9 g/dL (for pregnant women) and 8-10.9 g/dL (for no-pregnant women), and severe if the levels were below 7 g/dL (for pregnant women) and below 8 g/dL (for non-pregnant women).

Oktavianis et al. (2022) conducted a study to investigate the effect of chicken dim sum with moringa flour on hemoglobin levels in adolescent girls. The Hb levels were measured before and after the intervention for approximately one month using Easy Touch GcHb and an observation sheet for primary data collection. After the intervention, the Hb levels increased from 11.0 gr/dL to 11.5 gr/dL, indicating a positive effect of consuming chicken dim sum with *Moringa oleifera* flour on the hemoglobin levels of adolescent girls. Iron-rich foods can help prevent anemia, which also requires adequate protein. Proteins in red blood cells serves as carriers of carbon dioxide and oxygen and are essential for the formation of red blood cells. Moringa leaves are a highly nutritious food source, rich in iron and protein. Therefore, combining them with chicken dim sum is an effective way to increase iron intake[18].

Oktaria et al. (2018) in their study argued that there is a lack of systematic research on the relationship of poverty, nutrition, and leprosy. Despite the assumption that nutritional deficiencies may impair the body's immune response to *Mycobacterium leprae*, few studies have investigated this correlation. The study aimed to investigate the relationship between anemia and iron profiles in newly diagnosed leprosy patients in poor rural areas of Indonesia with a high proportion of multibacillary cases using interview methods. They found that individuals at high risk of developing leprosy had lower levels of education than the control population, suffered from anemia, and lacked access to a variety of food options due to inadequate staff. They measured anemia based on Hb levels and iron profiles using serum iron, TIBC, ferritin, and transferrin saturation. Iron deficiency was determined by high TIBC or low ferritin. The study did not find a significant correlation between iron deficiency and leprosy, although lepers often have low serum iron and high ferritin levels[19].

The screening for anemia is commonly done by clinical testing using cyanmethemoglobin method or HemoCue. Other methods used in developing countries include the filter paper method (including the WHO color score), copper sulfate method, and Sahli's method[12]. In addition to traditional laboratory methods, anemia can also be diagnosed by assessing hemoglobin (Hb) with point-of-care testing (POCT) devices, such as the HemoCue testing system. In certain healthcare settings where speed is of the essence, these devices can replace traditional laboratory testing. However, their use must adhere to basic standards, including regulatory, economic, and clinical considerations. Proper training of users on testing requirements, performance, limitations, and possible interferences, as well as frequent venous and arterial sampling are necessary. Rigorous quality assessment, performed by laboratory professionals, is also crucial[21].

To ensure accurate measurement of Hb, clinical laboratories and field settings use precise, high-quality measurement methods. Importantly, the field includes areas outside of a controlled environment. Factors to consider when assessing Hb levels include the blood sample, cost of analysis, and reproducibility of results. When choosing Hb measurement methods in a clinical or field laboratory, it is important to consider several factors, including quality control (QC), resource availability, and training standards. By taking these factors into account, the risk of negative impacts of Hb measurement can be reduced[22].

Hb levels are typically measured invasively by drawing a blood sample. The Sahli's method, a manual process, or the cyanmethemoglobin method, which uses a spectrophotometer are used to measure the color intensity of the blood sample. However, these methods are inefficient and painful for the patient because they require the patient to injure a finger. In addition, the process is lengthier due to the recording, collection, and recapitulation of Hb measurement results on a computer[23]. Various non-invasive screening methods have been developed in different countries. One of the methods, tested by Robert et al. (2018), uses nail images from a smartphone and does not require personalized calibration. Smartphone Hb levels were measured with a bias of only 0.2 g dL-1 in 100 patients with various anemia diagnoses mixed with healthy subjects, with a range of up to ±2.4 g dL-1. The study demonstrated that a non-invasive method for anemia screening had higher accuracy than existing invasive POC methods. Furthermore, receiver characteristic analysis showed that this test had strong diagnostic performance with an area under the curve of 0.88, indicating accuracy across the range of Hb levels tested[24].

In another study, Young et al. (2021) measured Hb using an application that captured all images using the default camera settings of the application's native camera on Android and iOS. The researchers noted any nail polish or discoloration, and if nail polish was found, it was removed with acetone and a cotton swab before the non-invasive assessment. Prior to imaging, the research participants were assigned identification numbers to be entered on the application and the background lighting was normalized using a consistent light source. All images were captured indoors, away from windows, and with a camera flash to minimize any variability in background lighting that could potentially affect Hb measurements. This smartphone application use the unpigmented nature of the nail to measure Hb levels by correlating nail color

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and specific imaging parameters with blood hemoglobin levels[25].

Anemia screening faces several challenges in practice, including insufficient funding for medical tests, lack of medical personnel and resources in remote areas, and patient's reluctance to be screened. Various anemia screening methods have been developed in different countries, including Indonesia, due to their affordability, ease of use, and non-invasive nature compared to commonly used invasive approaches[26]. However, the high prevalence of anemia has been attributed to measurement bias. Reliable assessment tools to measure and interpret Hb concentrations, as well as contributing factors to anemia in community and clinical settings, are needed to achieve global targets for reducing anemia and to evaluate the effectiveness of interventions[27].

Hemoglobin is a simple and convenient biomarker for determining the severity of iron deficiency, particularly in populations with high prevalence. However, it may not be specific enough because it can also be affected by vitamin B12 or folic acid deficiency, genetic disorders, or other chronic diseases. Therefore, it should be used in conjunction with other indicators to increase specificity. Serum transferrin, also known as ST, is a transport protein for iron and is commonly measured together with serum iron. The serum ferritin measurement method is highly sensitive and reliable for assessing iron stores in healthy individuals. While low serum ferritin levels indicate a deficit in iron stores, they do not always reflect the severity of the deficiency due to the high variation in measurements. Therefore, this method is often used for clinical assessments and field surveys. Combining hemoglobin and serum ferritin improves sensitivity and value specification. Normal values for both indicators indicate no iron deficiency. Moreover, transferrin receptor (STfR) can detect iron deficiency anemia (IDA) and iron deficiency in the body. The use of Stfr and SF indicators represents 85% of iron in the body and is the best indicator for measuring iron[28].

CONCLUSION

Combining hemoglobin and serum ferritin can increase sensitivity and specificity for detecting iron deficiency, as hemoglobin is a key indicator of the severity of iron deficiency. If both indicators are normal, there is no iron deficiency, as serum ferritin indicates iron stores and transferrin receptor indicates iron in tissues. The serum transferrin receptor indicator can be used for detection of both iron deficiency anemia (IDA) and iron deficiency in the body. Transferrin receptor and serum ferritin are the most reliable biochemical indicators for measuring iron levels in the body, accounting for 85% of total iron. It is important to use appropriate tools that meet the necessary requirements to avoid measurement bias, as this can affect the final result of hemoglobin levels and contribute to the high prevalence of anemia. To achieve the global target of reducing anemia and evaluating the effectiveness of interventions, reliable assessment tools are needed to measure and interpret Hb concentrations as well as anemia-causing factors in clinical and community settings and for follow-up evaluations.

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