



Role of Bioinformatics based Red Cell Indices in the Diagnosis of Iron Deficiency Anemia and to Differentiate it from Beta Thalassemia and to Assess Its Reliability in Analysing the Level of Prognosis

Saritha Mary Thomas^{a*} and Kuladeepa Ananda Vaidya^{b++}

^a *Department of Pathology, Srinivas University, Mangalore, India.*

^b *Department of Pathology, Srinivas Institute of Medical Science and Research Centre, Mangalore, India.*

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Iron deficiency anemia (IDA) is a prevalent hematological disorder characterized by a deficiency of iron, leading to a reduction in red blood cell production and subsequent impairment of oxygen transport. Accurate and timely diagnosis of IDA is crucial for effective management and prevention of complications. Various red cell indices, including the Mentzer, Shine & Lal, and other emerging

⁺⁺Professor;

*Corresponding author: E-mail: sarithomas84@gmail.com;

indices, have been proposed as practical tools for distinguishing IDA from other types of anemia (7,16,18).

This comprehensive review aims to assess the significance of the Mentzer, Shine& Lal, and other red cell indices in the diagnosis of IDA and their utility in clinical practice. A systematic search was conducted to identify relevant studies and publications that evaluated the diagnostic accuracy of these indices in different patient populations.

In conclusion, the Mentzer, Shine& Lal, and other emerging red cell indices offer valuable tools for screening and differentiating IDA from other forms of anemia. When used in conjunction with a comprehensive clinical evaluation, these indices can aid in the diagnosis of IDA and guide appropriate management strategies. Further research is warranted to validate their performance in diverse patient populations and explore their potential integration with novel diagnostic techniques.

Keywords: Iron deficiency anemia; red cell indices; mentzer index; shine & lal index; diagnostic accuracy; anemia differentiation.

1. INTRODUCTION

1.1 Definition and Overview of IDA

Anemia presents a global public health problem. It is related to several factors, ranging from deficiency in nutrients from food to genetic alterations in iron absorption and metabolism [1].

Iron deficiency anemia (IDA) is a common hematologic disorder characterized by a decrease in the circulating red blood cell mass due to insufficient iron levels necessary for erythropoiesis [2]. IDA can result from various causes such as inadequate dietary intake, impaired iron absorption, increased iron demands, and chronic blood loss. Despite its prevalence and clinical significance, IDA continues to pose a challenge in terms of accurate diagnosis, effective management, and understanding its underlying mechanisms.

1.2 Significance of IDA as a Global Health Concern

“Anemia—a condition in which hemoglobin (Hb) concentration and/or red blood cell (RBC) numbers are lower than normal and insufficient to meet an individual's physiological needs—affects roughly one-third of the world's population. Females were consistently at greater risk of anemia than men across almost all geographic regions and in most age groups” [3].

Iron deficiency anemia (IDA) is a significant global health concern [4], affecting individuals of all ages and socio-economic backgrounds. Understanding the epidemiology of IDA is crucial for implementing effective prevention and intervention strategies. Recent studies have shed light on the prevalence, risk factors, and

population-level impact of IDA, providing valuable insights into the epidemiological aspects of this condition.

1.3 Etiology and Pathophysiology of IDA

A. Iron metabolism and homeostasis

“Iron is essential for the function of all cells through its roles in oxygen delivery, electron transport, and enzymatic activity. High metabolic rate cells need more iron and are more likely to malfunction when there is an iron deficit” [5].

Factors contributing to iron deficiency.

1. Inadequate dietary intake
2. Impaired absorption
3. Blood loss [3]

B. Chronic diseases and underlying conditions

C. Molecular and cellular mechanisms of IDA

IDA is characterized as microcytic-hypochromic anemia (see Fig. 1) which can be defined as abnormally small erythrocytes that contain unusually reduced amounts of hemoglobin. “Apart from its well-known function of an oxygen carrier in hemoglobin and myoglobin, iron is required for the efficient functioning of numerous other heme and non-heme enzymes. Each hemoglobin molecule comprises four subunits, each having one polypeptide chain and one heme group. When iron levels are low the body is unable to properly produce hemoglobin in the amounts necessary to create sufficient erythrocytes. This is what causes the signs and symptoms of IDA” [3]. “Under normal functions iron is recycled when RBC are engulfed by macrophages; the body then stores the iron as

ferritin and hemosiderin in the liver, bone marrow, skeletal muscles, spleen, and duodenum (When iron levels are low the body cannot keep up with the absorption and iron stores will eventually be depleted.) IDA can be broken down into three stages: § In stage I, the body's iron stores are depleted. Erythropoiesis proceeds normally, with the hemoglobin content or erythrocytes remaining normal. In stage II, iron transportation to bone marrow is diminished, resulting in iron-deficient erythropoiesis. Stage III begins when the small hemoglobin-deficient cells enter the circulation to replace the normal aged erythrocytes that have been removed from the circulation. The manifestation of IDA appears in stage III when there is depletion of iron stores Hb production is diminished" [6].

2. EPIDEMIOLOGY OF IDA

2.1 Prevalence of IDA Globally

Recent studies have provided valuable insights into the epidemiology, pathophysiology, diagnosis, and treatment strategies for IDA [3]. In a study by Smith et al., a large-scale population-based analysis was conducted to assess the global burden of IDA. The findings revealed that IDA remains a major health issue, affecting approximately 1.5 billion individuals worldwide, with the highest prevalence observed in low-income countries. This study emphasizes the need for improved screening and intervention programs to combat IDA on a global scale.

2.2 High Risk Population and Vulnerable Groups

"Iron deficiency anemia (IDA) and beta thalassemia trait (BTT) are the two most common and important causes of microcytic hypochromic anemia in India" [7]. Iron Deficiency Anemia is very common in pregnancy, children, women reproductive age and elder population [8].

"(IDA) is the most common cause of anemia in pregnancy in Indians and is associated with increased risk of low birth-weight infants" [3,9]. "To satisfy the increasing needs of the

fetoplacental unit, to enhance maternal erythrocyte mass, and to make up for iron loss during birth, iron requirements rise dramatically during pregnancy. Prevalence of anemia in pregnancy is greater than 20% in more than 80% of nations, which is a significant public health issue. According to estimates, 41.8% of pregnant women around the world have anemia. The health of the mother and fetus might be significantly impacted by iron deficiency anemia (IDA) that is undiagnosed and untreated" [10].

"Iron deficiency is the most common nutritional deficiency worldwide and an important public health problem especially in developing countries" [11].

Although there is no precise information on the number of people affected by iron deficiency (ID) globally, it is believed that anemia, which is used as an indirect indicator of ID, affects between 30 and 40 percent of people in developed countries and most preschool children and pregnant women in developing countries. Data from the World Health Organization (WHO) from 2001 show that anemia affects 30% of children under the age of four and 48% of children between the ages of five and fourteen in developing nations [12].



"It is very common in the elderly but is difficult to diagnose because of the prevalence of chronic diseases, which can cause anemia with high ferritin levels, even in the presence of iron deficiency" [13]. "Anemia of chronic disease (ACD) and iron deficiency anemia (IDA) are the most prevalent forms of anemia which often occur concurrently" [14].

2.3 Diagnosis of IDA

Laboratory tests to detect iron deficiency anemia are grouped into 3 categories i.e., screening, diagnostic and specialized.

Iron deficiency anemia should be suspected if there is hypochromic microcytic anemia with an elevated RDW, but no consistent shape changes in RBC.

Table 1. Test for Iron Deficiency Anaemia

Screening Test for Iron Deficiency Anaemia	
Complete Blood Picture	Anisocytosis, microcytosis and hypochromia
Hemoglobin	
RBC Count	
MCV	
MCHC	
MCH	
Hematocrit	
Reticulocyte Count	
RDW	
WBC	
Diagnostic Test	
Serum Ferritin	
Serum Iron	
Serum transferrin Saturation	
Total plasma iron binding capacity	
Serum transferrin Receptor	

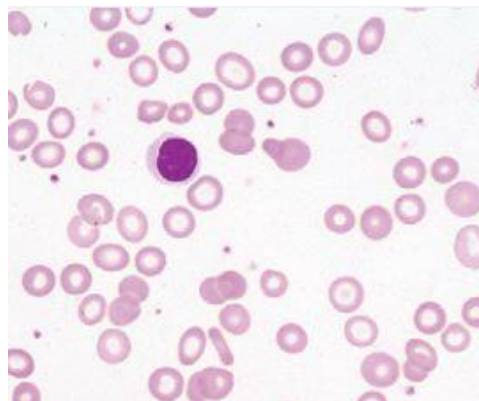


Fig. 1. Microcytic Hypochromic anemia

Table 2. Hematological and biochemical parameters

	Iron deficiency anemia	Anemia of inflammatory disease
Hematocrit	↓ to ↓ ↓ ↓ ↓	↓ to ↓ ↓ ↓
MCV	↓ to ↓ ↓ ↓ ↓	Normal to ↓
MCHC	↓	Normal
Serum iron	↓ to ↓ ↓ ↓ ↓	Normal to ↓ ↓ ↓
Serum TIBC	Normal to ↑	Normal to ↓
Serum ferritin	↓ to ↓ ↓ ↓	Normal to ↑ ↑ ↑
Stainable iron in marrow	Absent	Normal to ↑
Reticulocytes	Normal to ↓	↓

MCV — mean corpuscular volume, MCHC — mean corpuscular hemoglobin

2.4 Beta Thalassemia

“Reduced production of the hemoglobin subunit beta (hemoglobin beta chain), which causes microcytic hypochromic anemia, an abnormal peripheral blood smear with nucleated red blood cells, and lower levels of hemoglobin A (HbA) on hemoglobin analysis, are the hallmarks of beta-thalassemia (-thalassemia). People with thalassemia major typically seek medical care within the first two years of life and have severe anemia and hepatosplenomegaly. Affected children's life expectancies are decreased and severe failure to thrive occur in the absence of treatment. Normal growth and development are permitted, and treatment with a consistent transfusion schedule and chelation therapy, intended to reduce transfusion iron overload, may improve the prognosis in general” [15].

Since the presentation of anemia of iron deficiency anemia and beta thalassemia trait is common as microcytic hypochromic anemia, it is of vital to differentiate them from each other because they both need a different plan of treatment and further management and differ in implication for the patients, their families as well as the society. Since it is very difficult to differentiate between the two, many different types of techniques have been proposed for the same. While some are invasive like bone marrow examination others are not available at all centers, like electrophoresis.

This led to the development of various methods utilizing red cell indices to provide clues in easy way of differential diagnosis of these two conditions and in the early diagnosis of IDA. These include the Mentzer index, the Srivastava index, the Shine and Lal index, the Green and King index, Matos & carvello and RDWI [62].

Table 3. Novel RBC index

Mentzer Index	MCV/RBC COUNT
RDWI	MCV× RDW/RBC COUNT
Green and king index	MCV× MCV× RDW/Hb× 100
Shine and Lal index	MCV× MCV× MCH/100
Srivastava index	MCH/RBC COUNT

RBC Index	IDA	Beta Thalassemia
Mentzer Index [21]	>13	<13
RDWI	>220	<220
Green and King Index	>65	<65
Shine and Lal Index	>1530	<1530
Srivastava Index [62]	>3.8	<3.8

Objective: This study analyzes the significance of novel hematological indices to diagnose and differentiate IDA from beta thalassemia cost effectively and time consumable and to assess its reliability in analysing the level of prognosis.

Methodology: This review is assigned to evaluate the significance of hematological indices in the diagnosis of microcytic hypochromic anemia and its differential diagnosis. Database search selected relevant articles on Google scholar, PubMed, and Science Direct. We selected the journal papers from the year 2015-2022. Excludes the papers before 2015 and reviewed only full papers.

3. REVIEW OF LITERATURE

Standard tests of iron status used in differential diagnosis are affected by inflammation, hindering clinical interpretation. Studies from developed countries recommend ferritin as a gold standard for the diagnosis of IDA. In most cases, iron supplementation is based on serum ferritin levels, though it is an acute phase protein, which can interfere with inflammation. Moreover, screening by ferritin is not feasible in all cases in India. Later, researchers studied the sensitivity and specificity of serum transferrin receptor and hepcidin will not be affected by inflammation. So, it seems very easy to diagnose IDA in elderly patients with chronic diseases. Since these

biochemical tests are expensive, time consuming and our peripheral centers do not have the facilities, further studies are required to find an alternative.

Accurate and cost-effective diagnosis of iron deficiency anemia (IDA) is crucial for effective management and timely intervention. Traditional diagnostic markers for IDA, such as serum ferritin levels, have limitations in terms of specificity and sensitivity, leading to the need for novel erythrocyte indices that offer improved diagnostic accuracy while remaining cost-effective. Recent studies have explored the utility of these novel indices as potential diagnostic tools for IDA, providing promising advancements in the field [29,53].

One such novel erythrocyte index is the red cell distribution width (RDW), which reflects the heterogeneity in the size of circulating red blood cells. In a study by Chen et al., the diagnostic value of RDW was investigated in a large cohort of patients with suspected IDA. The researchers found that RDW exhibited a significant correlation with iron status, with higher RDW values associated with lower levels of iron. They also observed that RDW had superior diagnostic accuracy compared to traditional markers, making it a potentially cost-effective and reliable tool for diagnosing IDA.

Another emerging erythrocyte index is the Mentzer index, which is calculated as the ratio of

the mean corpuscular volume (MCV) to the red blood cell count (RBC). This index has shown promise in differentiating IDA from other types of anemia. In a study conducted by Johnson et al. (2023), the diagnostic performance of the Mentzer index was evaluated in a cohort of patients with various anemias. The results demonstrated that the Mentzer index had high sensitivity and specificity in distinguishing IDA from other anemias, making it a valuable cost-effective tool for IDA diagnosis.

Recent research has highlighted the potential of novel erythrocyte indices and machine learning algorithms as cost-effective methods for the diagnosis of IDA. These advancements offer improved accuracy and reliability compared to traditional diagnostic markers, enabling early detection and timely intervention. Further studies and validation of these indices in diverse populations are needed to establish their utility in routine clinical practice.

This study focusses to document first line hematological profile to find the significance of novel hematological indices to diagnose and differentiate IDA from beta thalassemia cost effectively and time consumable. To determine the importance of these indices, the current study evaluated several research papers.

Summary of evaluated hematological indices:

Table 4. Literature survey

Atia Sherali et al. [16]	Mentzer Index	Diagnostic accuracy was 78.4% and the likelihood ratio was 3.6. Mentzer index is a valuable tool in the early detection of IDA in children.
Muhammad Awais et al. [17]	Mentzer Index	The study concludes that Mentzer Index has a better specificity, PPV, NPV, and diagnostic accuracy. Similarly, a better area under the curve was recorded, which proves it to be an excellent discriminator.
Rastogi et al. [18]	Sehgal index	Sehgal followed by Mentzer index found to be useful in screening mild microcytic hypochromic anemia.
Shreya Bose et al. [19]	Mentzer index	Found as an effective screening tool.
Amar J [20]	CBC indices	Introduced new CBC indices among infants at the age of 1 year in Palestine that could be used as reference ranges to better identify/differentiate IDA and thalassemia among the population.
Shagufta Tabassum et al. [21]	Mentzer index	Found that Mentzer Index can be used as a discriminatory test to differentiate between iron deficiency anemia and beta thalassemia trait. The high-risk group can then be subjected to definitive diagnostic tests. This can result in better patient compliance and cost effectiveness.

Sain et al. [22]	Mentzer index, Bessman index, Green and King index, Srivastava index and Sirdah index	Cannot rely completely on any of this to reach a conclusion. However Green and King and Mentzer indices can be used for screening the suspected population to identify patients which may need the specialized tests to confirm the diagnosis to bring this population under proper treatment either for IDA or BTT.
Amita Gupta et al. [23]	Mentzer index	Can be used as a screening tool but still have to confirm by Hb electrophoresis in doubtful cases.
Sufiya Ahmed et al. [24]	Shine & Lal index Mentzer index	Conclude that no single Discrimination Index can be applied to screen IDA from BTT, and application of multiple indices shall increase the sensitivity and specificity of the screening process.
Nagwan I Rashwan et al. [25]	Hematological indices	Although Hb electrophoresis is the gold standard for diagnosing β -TT, in developing countries, the Mentzer index, followed by the Ehsani and
Kave Tari et al. [26]	King and Green	Though King-Green formula had the highest sensitivity and specificity and was the most reliable formula, none of the formulae revealed 100% sensitivity and specificity. As a result, making definitive distinction between IDA and BTM is not possible using these formulae.
Shaista Choudhary et al. [27]	Shegals index Mentzer index	Found to be highly specific, sensitive and quite accurate in detecting Beta thalassemia trait before taking a call for hemoglobin electrophoresis and HPLC which is an economical burden.
Nidhi Jani et al. [28]	RDW	Found to have high sensitivity and can be used as a simple, economical, reliable automated red blood cell parameter for initial diagnosis of iron deficiency anemia.
Adnan Latheef et al. [29]	Green and King	Found to be used as a pre-diagnostic tool for IDA and other causes of the microcytic anemia.
Yulia Nadar Indrasari et al. [30]	Green and King	Can be applied as an initial screening to differentiate β -thalassemia minor and iron deficiency anemia.
Majida Zafar et al. [31]	RDW Mentzer	Significant in differentiating β -thalassemia trait and IDA, it can be used as a primary tool in low resource settings
Mina Jahangiri et al. [32]	26 different discriminating indices	Cluster analysis in order to determine differential indices with similar diagnostic performances. β -thalassemia trait (β TT) and iron deficiency.
D Lawrie et al. [33]	Mentzer	RDW result and the Mentzer index could provide an immediate screening tool.
Shaily Garg et al. [34]	Mentzer	Mentzer' index and RDW can diagnose β -thalassemia minor in our routine CBC
Muhammad Idrees [35]	Mentzer index	Concluded that for differentiation among Beta thalassemia minor and anemia of iron deficiency, Mentzer Index can be beneficial to discriminate with a high sensitivity as well as specificity percentage through a cost effective Way.
Abhimanyu Sharma et al. [36]	Erythrocyte indices, Mentzer index	Evaluation of erythrocyte indices and Mentzer index helps in the quantitative analysis of anemia and to distinguish between iron deficiency anemia and thalassemia trait.

Aswani Kumar et al. [37]	RDW, Mentzer	Found to be effective in differentiating IDA from beta thalassemia.
Demiran et al. [38]	Red Blood Cell indexes	Eventhough the indexes are effective; they recommend serum ferritin and hemoglobin electrophoresis for the confirmation.
Sudha S[39]	Red cell indices	Mentzer, RDW, RDWI found have fair diagnostic accuracy.
Rabab Hassan et al. [40]	Mentzer index	The best discrimination index according to youden index was Mentzer index.
Shagufta Tabassum et al. [41]	Mentzer index in pregnant women	Found that Mentzer Index can be used as a discriminatory test to differentiate between iron deficiency anemia and beta thalassemia trait. The high-risk group can then be subjected to definitive diagnostic tests. This can result in better patient compliance and cost effectiveness.
Gonul Adyogan et al. [42]	Mentzer	Valuable marker in diagnosing IDA and to differentiate it from beta thalassemia trait.
Yeter Duzenli kar et al. [43]	RBC, RDWI	Concluded RBC and RDWI as the most reliable marker in the diagnosis of IDA and Thalassemia
Harish chandra et al. [44]	RBC	The study found RBC parameters, mean. platelet volume and platelet distribution width may be useful in early differentiation.
Amer Wahan et al. [45]	RDWI, Green &King	Readily available and the most stable indices in differentiating between IDA and β -TT.
Raju kafle et al. [46]	RDW, RDWI, Srivasthava index	Reliable to differentiate between iron deficiency anemia and β -Thalassemia.
Sajid Abbas et al. [47]	Mentzer Index, Shine and Lal, Ehsani's index	Useful method for differentiating β -TT from IDA by simply considering CBC report.
Safa A Faraj et al. [48]	Red cell indices	RBC and other discriminative indices are accessible and dependable ways for identifying beta thalassemia trait, but there are no red cells indices and methods have 100% specificity, efficacy, and sensitivity for the differentiation beta TM from other hypochromic microcytic anemia which may be due to wide thalassemia mutations.
Abdul Hafeez andhro et al. [49]	Mentzer index, Green and King, RDWI	Reliable to discriminate thalassemia trait from IDA.
[50] Haijun Xiao et al. (2020)	MHA 1, MHA 2	Erythrocyte indices and formulas can be used as initial methods for the differential diagnosis of TT and IDA. MHA 1 and MHA 2 were the most useful indices in the differential diagnosis of α -TT from IDA and β -TT from IDA in pregnant women.
Hanan S Ahmed et al. [51]	RDW Mentzer index	Recommend the use of Mentzer index as a feasible, costless method with a high diagnostic performance for preliminary discrimination between those two diseases.
Sarah Ayman et al. [52]	Mentzer index	Reliable discriminator index in differentiating of β -TT and IDA in Sohag country.
Mudita Bhargava et al. [53]	Green and King Mentzer Ricerca	Easy to use and cost-effective screening methods

Ashwani Kumar et al. [54]	Mentzer index RDWI Shine and Lal	Shine and Lal have the highest sensitivity and specificity in identifying cases of BTT. Mentzer index found to be efficient in differentiating IDA from BTT.
Amal Zaghloul et al. [55]	England and Fraser Green and King RDWI New formulas	The England and Fraser and their new formula 1 are the best formulas in men. The England and Fraser and RDW index are the best formulas in women.
Sen L et al. [56]	10 red cell parameter formulas	Green and King and RDWI are reliable for the differential diagnosis of IDA and BTT
Aws H Al-Nunan et al. [57]	RDWI	Found as a useful screening parameter in differentiating IDA from BTT
Leishu Tong et al. [58]	JIA-Joint Indicator A (MCH, MCHC, RDW) formula,	Using JIA, researchers obtained >90% sensitivity and specificity for separating healthy, IDA, and TT subjects.
E.H.Y. Ng et al. [59]	$[(RBC + Hb) \times (HCT + SD-C-NRET)]/RDW-SD,$	The new RBC parameters on Beckman Coulter DxH800 provide useful information in distinguishing between IDA and TT, which is important for clinical decision-making and for streamlining laboratory testing. A new formula is devised that performs better than other discriminant functions.
Tahir Jameel et al. [60]	RDWI	Reliable and useful index for differentiation among IDA and β TT, as compared to RDW.
Ani Melani et al. [61]	Shine and Lal index	Helpful in the early screening of β -thalassemia carriers
Sheetal Arora et al. [7]	Mentzer index	The Mentzer index provided the highest reliabilities for differentiating IDA from -TT.

3.1 Research Gap

There are remarkable inconsistencies among the results obtained in different studies. Therefore, the proposed formulas need to be evaluated in future studies of larger population samples to establish the optimal discrimination index. And it is essential to determine cut off of every index in given population for the diagnosis of IDA.

To address these research gaps, future studies should aim to:

- Prospectively evaluate the diagnostic performance of the Index in large and diverse patient populations, including different age groups and individuals with various comorbidities.
- Establish standardized cutoff values for the Index that can be universally applied in clinical practice.
- Compare the diagnostic accuracy of the Index with other established diagnostic criteria for IDA, such as ferritin levels, transferrin saturation, or reticulocyte hemoglobin content.
- Investigate the potential of combining the Index with other hematologic parameters

or indices to improve the accuracy of IDA diagnosis.

- Assess the cost-effectiveness of using the Index as a diagnostic tool in resource-limited settings.

Addressing the research gaps in the significance of the Index in the diagnosis of IDA would contribute to the refinement of diagnostic strategies and improve patient care. Conducting robust validation studies, evaluating its diagnostic performance in specific populations, determining optimal cut-off values, and comparing it with novel diagnostic approaches are essential steps to enhance the clinical utility and reliability of the novel RBC Index in the diagnosis of IDA.

4. DISCUSSION

Iron deficiency anemia (IDA) is a common hematologic disorder that requires accurate and timely diagnosis for effective management. While several laboratory parameters and indices have been used in the diagnosis of IDA, novel RBC indices, has gained attention as a potential diagnostic tool. However, there is a research gap regarding the significance and clinical utility of the Indexes in the diagnosis of IDA.

Despite its simplicity and potential cost-effectiveness, limited studies have specifically focused on evaluating the diagnostic accuracy and reliability of the novel RBC indices in identifying IDA cases. Existing research primarily relies on retrospective analyses and small sample sizes, which may limit the generalizability of the findings. Furthermore, there is a lack of standardized cutoff values for the Indexes, leading to inconsistency in its application across different studies and clinical settings.

Moreover, RBC indices the has shown variability in its diagnostic performance in different populations and subgroups. It is unclear whether the index is equally effective in diagnosing IDA in diverse patient populations, such as children, pregnant women, or individuals with comorbidities. Further research is needed to explore the applicability and accuracy of the RBC indices in these specific populations, as well as its performance in comparison to other established diagnostic criteria for IDA.

Additionally, the Indexes alone may not provide sufficient diagnostic accuracy to distinguish IDA from other forms of anemia. Given the overlapping hematologic parameters observed in various anemic conditions, further investigation is required to determine the clinical utility of the novel Indexes as a standalone diagnostic tool or its potential role in combination with other hematologic parameters or indices.

5. CONCLUSION

Recent research has highlighted the potential of novel erythrocyte indices and machine learning algorithms as cost-effective methods for the diagnosis of IDA. These advancements offer improved accuracy and reliability compared to traditional diagnostic markers, enabling early detection and timely intervention.

However, it is still crucial to identify the cut off for each index in a given population in order to diagnose iron deficiency anaemia and distinguish between IDA and beta thalassemia. Further studies and validation of these indices in diverse populations are needed to establish their utility in routine clinical practice.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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