Validity of Red Cell Distribution Width Versus Red Cell Distribution Width Index to Differentiate between Iron Deficiency Anemia and β-Thalassemia Trait in an Adult Omani Population: A Cross-sectional Study Contagiosity: A Review

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Abstract

Introduction: Iron deficiency anemia (IDA) and β-thalassemia trait (BTT) are the two most frequent causes of microcytic anemia; however, differentiation between these conditions is of clinical importance for treatment purposes. The aim of this study was to determine the reliability of red cell distribution width (RDW) versus red cell distribution width index (RDWI) as hematological discriminator indices to differentiate between IDA and BTT in an adult Omani population.

Methods: This cross-sectional study was conducted in 2019 at various primary health care centers in Muscat Governorate, Oman. A retrospective review was conducted of adult Omanis participating in the national premarital screening program. Identification of IDA and BTT was performed according to the diagnostic criteria of the World Health Organization. Subsequently, the validity of RDW and RDWI as discriminator indices to differentiate the two conditions were evaluated according to their sensitivity, specificity, positive predictive value, negative predictive value, and Youden's index (YI). In addition, a receiver-operating characteristic (ROC) curve analysis was performed to calculate the area under the curve (AUC).

Results: A total of 156 cases (15.5%) of IDA and 113 cases (11.3%) of BTT were identified among 1,004 individuals undergoing premarital screening. Neither of the two discriminator indices showed sensitivity and specificity rates of 100% and both had low YI values of <0.5. However, the AUC for RDWI was 0.81 compared to 0.62 for RDW. Conclusions: RDWI appears to be a good discriminator index to differentiate IDA from BTT.

Keywords: Iron Deficiency Anemia; beta-Thalassemia Trait; Red Cell Indices; Discrimination indices; Oman

Introduction

According to the World Health Organization (WHO), anemia is a very common health problem affecting more than 1.62 billion people worldwide, equivalent to almost a quarter of the entire global population [1]. While the exact prevalence of anemia among Omani adults is still unknown, rates of the condition are high in the Eastern Mediterranean region, particularly among women and children [2,3]. One study conducted at a tertiary hospital in Oman indicated that 91 out of 360 asymptomatic university students (26%) had iron deficiency anemia (IDA), of which 87 (95.6%) were female [4].

Microcytic hypochromic anemia may occur due to a wide range of causes, such as iron deficiency, hemoglobinopathies, and chronic diseases [1]. In particular, IDA results from a lack of iron, an essential substance in hemoglobin (Hb) synthesis [5]. This deficiency can occur as a result of the insufficient intake, poor absorption, or increased loss of iron [6]. In turn, the β-thalassemia trait (BTT) is another important differential diagnosis of microcytic anemia [7]. Thalassemias are genetic blood disorders that cause a reduction in either the α or β chains of Hb. According to findings from the Genetic Blood Disorders Survey, the prevalence of BTT in Oman was 2% in children under the age of 5 years in 2003, while the prevalence of homozygous β-thalassemia was 0.07% [8].

From a clinical perspective, discrimination between IDA and BTT is crucial. The direct effect of IDA on HbA2 level affects both the diagnosis of anemia etiology as well as the course of treatment, given that iron therapy is vital for patients with IDA but unnecessary for those with BTT. Furthermore, simple differentiation methods minimize the need for superfluous investigations which can be both costly and time consuming [7]. Currently, several definitive diagnostic indices are used to differentiate between IDA and BTT, including HbA2 level as well as serum iron and ferritin concentrations [9-11]. In addition, many red cell indices have been proposed as simple and cost-effective measures of discrimination between the two conditions; in other words, assessment of the ability of the index to diagnose patients with and without the disease or condition [12-15].

A previous study reported that various red blood cell indices - including red blood cell count (RBC), Hb level, hematocrit, mean cell volume (MCV), and mean cell Hb concentration - were significantly lower in patients with IDA compared to those with BTT, whereas red cell distribution width (RDW) was significantly higher (P <0.001) [7]. In turn, a recent prospective cross-sectional study of an adult population in Saudi Arabia undergoing premarital screening found that RDW index (RDWI) showed better sensitivity (94.0%) and specificity (88.0%) compared to RDW in the diagnosis of BTT; moreover, for IDA, sensitivity and specificity rates were 88.0% and 86.0%, respectively [16].

This study aimed to determine the reliability of RDWI compared to RDW to differentiate between IDA and BTT in an adult Omani population subjected to premarital screening. In most countries, the purpose of premarital screening is to test for common genetic blood disorders in a specific individual to determine the risk of transmitting such diseases to his/her future offspring [17]. In Oman, the Ministry of Health has operated a national premarital screening and counseling program since 1999 as a cost-effective preventive measure to reduce the incidence of congenital anomalies and inherited blood disorders [18]. This screening is integrated into primary health care (PHC) services throughout the country. Subsequently, genetic counseling is provided at health institutions such as a health center, polyclinic, or secondary or tertiary hopital by a genetic counselor/ trained health care provider. [18].

Methodology

This cross-sectional study involved a retrospective analysis of blood tests performed on healthy adults undergoing premarital screening in 2019 at various PHC centers in Muscat Governorate, Oman. Data were collected initially as secondary data from the national electronic health system database. However, the data received were not complete during this period for many health centers due to problems with the servers resulting in the data not being stored properly. Accordingly, the research team decided to collect additional data directly from the health centers. The necessary minimum sample size for the study was calculated to be 872 patients using Power Analysis and Sample Size Software (NCSS LLC, Kaysville, UT), based on the screening design and overall predictive power (i.e. sensitivity and specificity) designated during a pilot study.

Each health center in Muscat Governorate maintains a continuous record of all patients who have undergone hematological screening as a result of the national premarital screening program since its inception in 1999. As such, the research team reviewed all premarital hematological investigations performed for each patient during the study period. Only patients for whom there was a complete record of all necessary bloodwork investigations were included in the analysis, including a complete blood count (CBC), hemoglobin electrophoresis, sickling, and ferritin levels. All CBC results were measured using automated analyzers. For the purposes of the current study, IDA was diagnosed according to the WHO criteria based on low Hb levels (<13 g/dL in males and <12 g/dL in females), low ferritin levels (<30 ng/dL), and reduced MCV (<80 fL).[5] For ferritin levels, a cut-off value of 30 instead of 15 ng/dL was used because this has been found to improve sensitivity from 25% to 92%, while maintaining high specificity at 98% [6,19,20]. A diagnosis of BTT was based on elevated HbA2 concentrations (≥ 3.5%) and reduced MCV (<80 fL).

Subsequently, RDW and RDWI was calculated based on the parameters provided by the automated analyzer and according to the reference standard differential cut-off values outlined in Table 1 [21,22]. The validity of these two indices in the discrimination between IDA and BTT was then evaluated according to sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Youden's index (YI). In addition, a receiver-operating characteristic (ROC) curve analysis was performed to calculate the area under the curve (AUC) for each index. An AUC value of 1 indicates perfect diagnostic discrimination, while a value of 0.5 suggests no discrimination. For the purposes of the current study, AUC values of 0.5-0.7, 0.7-0.8, 0.8-0.9, and >0.9 were considered poor, acceptable, excellent, and outstanding, respectively [23].

Analysis of the data was carried out using the Statistical Package for the Social Sciences (SPSS) software, version 23 (IBM, Armonk, NY). Ethical permission for the study was granted by the Center of Studies and Research at the Ministry of Health in Oman. The second stage of data collection in which the researchers contacted individual health centers occurred with the approval of and facilitation from the Directorate General of Health Services for Muscat Governorate.

Results

Complete hematological data were available for a total of 1,004 healthy adult Omanis who underwent premarital screening during the study period at various PHC centers in Muscat Governorate. Of these, 156 cases (15.5%) of IDA and 113 cases (11.3%) of BTT were diagnosed based on the previously outlined WHO criteria. A flowchart of the patient selection and identification process is shown in Figure 1.

The median age and hematological parameters of the study groups are displayed in Table 2. Median levels of serum ferritin were 12.99 and 67 g/dL in the IDA and BTT groups, respectively, whereas median HbA2 concentration was 2.6% and 4%, respectively. Median Hb levels were

Table 1: Reference standard differential cut-off values for RDW and RDWI as discriminator indices between IDA and BTT.

Index	Author and year of reference	Calculation	Cut-off value for BTT	Cut-off value for IDA
RDW	Bessman *et al*. [21] (1979)	RDW	<14%	>14%
RDWI	Jayabose *et al*.[22] (1999)	$\frac{MCV \times RDW}{RBC}$	<220	>220

BTT = β-Thalassemia Trait, IDA = Iron Deficiency Anemia, MCV = Mean Cell Volume, RBC = Red Blood Cell Count, RDW = Red Cell Distribution Width, RDWI = Red Cell Distribution Width Index

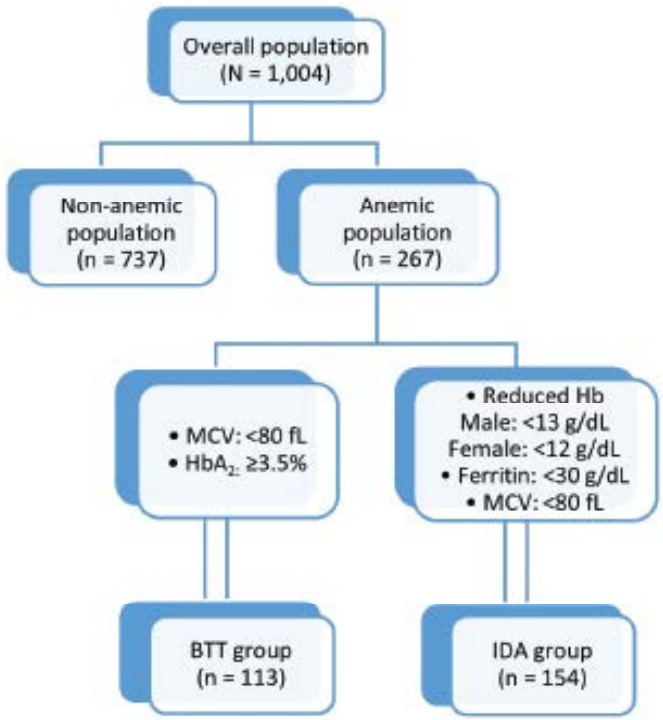

Figure 1: Flow chart of the patient selection process to identify IDA and BTT cases according to the WHO diagnostic criteria [5].

BTT = β-Thalassemia Trait, Hb = Hemoglobin, IDA = Iron Deficiency Anemia, MCV = Mean Cell Volume, WHO = World Health Organization.

lower in the IDA group compared to the BTT group (11.05 versus 12.7 g/dL). However, median MCV values were comparable in both groups (69.05 versus 68.3 fL). The IDA group had a lower median RBC compared to the BTT group at 4.89 and 5.66 × 106/μL, respectively. Finally, the median RDW was higher in the IDA group versus the BTT group (16.6% versus 15.8%), as was the median RDWI (228.24 versus 188.15). A comparison of the IDA group with the overall population revealed significant differences for all variables (P <0.05). The same was true for the BTT group for all variables except for age and Hb and serum ferritin levels.

The sensitivity, specificity, PPV, NPV, and YI of RDW and RDWI as discriminator indices are shown in Table 3 according to selected cut-off values. Overall, the RDWI demonstrated better sensitivity for the discrimination of BTT (83.18%), in contrast to RDW which had greatest sensitivity for the detection of IDA (93.66%). The highest specificity rate was obtained using RDW for the discrimination of BTT (69.58%). However, both discriminator indices had low YI values of <0.5. Nevertheless, when the cut-off value was decreased to 199, both the sensitivity and NPV of RDWI increased to 85.7% and 96.92%, respectively, for the detection of IDA. Similarly, the specificity of RDW as a discriminator index for the detection of IDA increased to 80.69% when the cut-off value was raised to 16.1%. High NPV rates persisted for both groups when the cut-off value for RDW was increased (92.07% and 81.15%, respectively).

A ROC curve analysis was conducted using a cut-off value of 199 for RDWI and 16.1% for RDW. Figure 2, AUC values for RDWI and RDW were 0.81

Table 2: Differences in hematological parameters and age according to group allocation (IDA and BTT).

Parameter	Median (IQR)		*P* value	Median (IQR)	*P* value
	Total population (N = 1,004)	IDA group (n = 154)		BTT group (n = 113)	
Age (years)	26 (7)	25 (7)	0.033	27 (6)	0.753
Hb (g/dL)	12.7 (2.15)	11.05 (1.3)	<0.001	12.7 (1.9)	0.059
MCV (fL)	74.45 (10.7)	69.05 (8.75)	<0.001	68.3 (10.25)	<0.001
RBC (× 10^6/μL)	5.28 (0.98)	4.89 (0.68)	<0.001	5.66 (1.06)	<0.001
RDW (%)	14.9 (2.5)	16.6 (2.4)	<0.001	15.8 (2.35)	<0.001
Ferritin (g/dL)	53 (101)	12.99 (12.04)	<0.001	67 (99.85)	0.13
HbA_2 (%)	2.7 (0.4)	2.6 (0.4)	0.014	4 (1.2)	<0.001
RDWI	207.86 (50.67)	228.24 (48.32)	<0.001	188.15 (41.47)	<0.001

BTT = β-Thalassemia Trait, Hb = Hemoglobin, IDA = Iron Deficiency Anemia, IQR = Interquartile Range, MCV = Mean Cell Volume, RBC = Red Blood Cell Count, RDW = Red Cell Distribution Width, RDWI = Red Cell Distribution Width Index.

Table 3: Sensitivity (TPR), specificity (TNR), PPV, NPV, and YI for RDW and RDWI as discriminator indices in the differentiation between IDA and BTT.

Index	Differential value	Group	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's Index
RDWI	>220	IDA	56.49	66.94	23.64	89.46	0.23
	<220	BTT	83.18	39.16	14.78	94.84	0.22
	>199	IDA	85.7	44.35	20.75	96.92	0.3
	<199	BTT	65.5	63.5	18.55	93.55	0.29
RDW	>14%	IDA	93.66	32.95	22.28	96.20	0.27
	<14%	BTT	13.86	69.58	5.9	85.43	-0.17
	>16.1%	IDA	61.69	80.69	36.54	92.07	0.42
	<16.1%	BTT	56.64	23.68	8.6	81.15	-0.2

BTT = β-Thalassemia Trait, IDA = Iron Deficiency Anemia, NPV = Negative Prediction Value, PPV = Positive Prediction Value, RDW = Red Cell Distribution Width, RDWI = Red Cell Distribution Width Index, TNR = True Negative Rate, TPR = True Positive Rate, YI = Youden's Index.

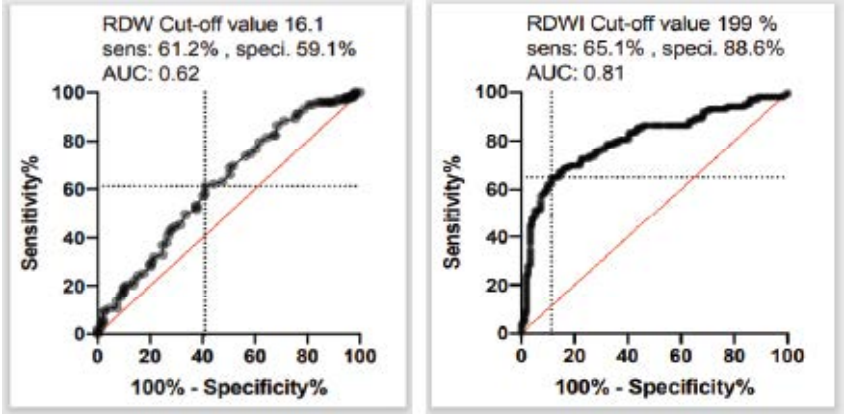

Figure 2: ROC curve plots showing the AUC for RDWI and RDW as discriminator indices in the differentiation between IDA and BTT.

AUC = Area Under the Curve, BTT = β-Thalassemia Trait, IDA = Iron Deficiency Anemia, RDW = Red Cell Distribution Width, RDWI = Red Cell Distribution Width Index, ROC = Receiver-Operating Characteristic, sens = Sensitivity, speci = Specificity.

and 0.62, respectively, thus indicating that RDWI was a better and more appropriate diagnostic discriminator index than RDW to differentiate between IDA and BTT in our population.

Discussion

According to the WHO criteria, anemia is defined by a blood Hb value of <7.7 mmol/L (13 g/dL) in men and 7.4 mmol/L (12 g/dL) in women; however, serum ferritin measurement remains the preferred method for detecting depleted iron stores in cases of IDA [5,6]. Nevertheless, previous studies have utilized varying cut-off values of serum ferritin to diagnose IDA. For instance, both Jameel et al. and Nesa et al. used ferritin values of <12 ng/mL, whereas Soliman et al. and Jahangiri et al. used values of <15 and <28 ng/mL, respectively [24-27]. This wide variation in serum ferritin criteria for the diagnosis of IDA could affect sensitivity rates of discriminator indices when differentiating between IDA and BTT. In contrast, the majority of these previous studies used an HbA2 concentration of >3.5% to diagnose BTT, as was the case in our study as well [25-27]. However, Jameel et al. used an HbA2 concentration of >3.2% to detect BTT cases among 620 adults undergoing premarital screening [24].

In the current study, the IDA group demonstrated low median Hb and RBC values, but higher median MCV, RDW, and RDWI values. Multiple studies have reported similar findings [26,28,29]. Rosatelli et al. concluded that HbA2 levels were not related to the severity of the mutation in BTT cases of Italian descent and that this factor varied among individuals with different mutations [30]. On the other hand, Rund et al. found that MCV was directly related to BTT mutation severity among a group of adults and older children of multiple ethnicities in Israel [31]. In addition, IDA can cause a decrease in HbA2 level, which could confuse the diagnosis and cause BTT to be overlooked if both conditions coexist in a single patient [32]. These factors could affect the use of standardized cut-off values for discriminator indices and explain reported variations when these indices are used in different populations. As such, further research is needed in order to determine appropriate cut-off values for discriminator indices in the Omani population.

The theoretical foundation for the use of RDW as a discriminator index is as a measurement of the degree of anisocytosis in the red blood cells, with this being usually high in IDA and near normal or only mildly increased in BTT. Some studies have found RDW to be a useful discriminator index in differentiating between IDA and BTT [33-35]. However, in our study, RDW resulted in low YI and AUC values (<0.3 and 0.62, respectively), thus indicating this index to be a poor discriminator, despite its high sensitivity (93.66%) and NPV (96.2%) in the detection of IDA, as well as the significant difference in median values between IDA and BTT (16.6% versus 15.8%; P <0.001). Most previous studies have used cut-off points of 14% to discriminate between IDA and BTT using RDW [24,25,27]. Calculating the AUC for RDW in our study showed the maximum value occurred with a cut-off point of 16.1%, a value considerably higher than that used in our reference standard [21]. Nevertheless, despite using this higher cut-off point, the AUC value remained low at 0.62, signifying that RDW was a poor discriminator index in our population [23].

In line with these findings, Mohammed et al. reported that RDW had limited value for discriminating between IDA and BTT among a cohort of Egyptian children (AUC: 0.553), with a non-significant difference in mean RDW values between the two groups, despite using an even higher cut-off value (16.4%) [36]. Comparable results have also been reported among other populations in Saudi Arabia and India [24,33]. Furthermore, a study conducted in Iran evaluating 10 different discriminator indices found that red cell indices were affected by BTT mutation type, a factor which would hinder use of the same cut-off values for different populations prone to unique or different mutations [37]. Soliman et al. found that RDW at a cut-off point of 14.5% was able to differentiate BTT from IDA among 200 samples with microcytosis with 83.3% sensitivity and 100% specificity; however, MCV at 73 fL or less demonstrated better discrimination at 91.7% sensitivity and 100% specificity [26].

In our study, a higher AUC value of 0.81 was obtained for RDWI at a cut-off point of 199, thus indicating RDWI to be an excellent discriminator index for the differentiation of IDA and BTT at this threshold [23]. This finding was supported by the significant difference in median RDWI values between the IDA and BTT groups (228. 24 versus 188.15; P <0.001). Despite using a lower differential cut-off point compared to our reference standard, the sensitivity of RDWI in detecting IDA increased from 56.49% to 85.7% [22]. Similarly, the NPV increased from 89.46% to 96.92%. In contrast, the sensitivity of this index for detecting BTT dropped from 83.18% to 65.5%, despite maintaining a NPV rate of >90%. In turn, the YI value increased only minimally from 0.22 to 0.29.

In comparison, Demir et al. reported a YI of 0.8 using a cut-off value of 220 for RDWI, concluding that this index was one of the most reliable discriminator indices for the differentiation of BTT and IDA [38]. Despite reporting a lower YI (0.65), Nesa et al. also judged RDWI to be both reliable and useful and a better index than RDW in differentiating between the two conditions [25]. In a study of a mixed Sistani and Baloch population from Iran, Miri-Moghaddam et al. found a cut-off value of 212 to result in the highest accuracy (i.e. resulting in the greatest sum of sensitivity combined with specificity), with an AUC value of 0.819 [37]. The researchers also suggested a need to determine appropriate cut-off values for each discrimination index in different populations due to the effect of BTT mutations on red cell indices [37]. Likewise, Fonseca Motas et al. concluded that RDWI appeared to be a reliable and useful index for the initial screening of microcytic hypochromic anemia in a Brazilian population and was better than RDW in differentiating IDA from BTT, with an AUC value of 0.912 [39].

There are several limitations to the current study. First, cases in which both IDA and BTT were suspected to co-exist in a single patient were not excluded from the analysis. Second, the sample size was relatively small. Further research is needed, particularly studies involving a larger sample size and the evaluation of additional discriminator indices in the Omani population. Moreover, a larger sample would help to more accurately determine appropriate cut-off points for such indices in this specific population.

Conclusion

Based on the findings of this study, RDWI was an excellent discriminator index to differentiate between IDA and BTT in an Omani adult population, resulting in an AUC value of 0.81 at a differential cut-off of 199. In turn, RDW was a poor discriminator, even after adjusting the cut-off value from 14% to 16.1%. Additional research is recommended in order to more accurately confirm appropriate cut-off values for red cell indices in the general Omani population.

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