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The cut-off values of discriminator indices for screening of beta-thalassemia trait

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Abstract

Background: β-thalassemia trait (BTT) can be screened by several discriminator indices (DIs) using complete blood counts (CBC). These DIs can help differentiate BTT from other causes of anaemia, thus reducing the financial burden of laboratory testing. At standard cut-off values, statistical analyses traditionally used to compare the diagnostic competence of these DIs give variable results. This study establishes new optimal cut-off values to improve the applicability of these DIs for BTT screening.

Methods: This was a retrospective study conducted on anaemic adults whose high-performance liquid chromatography (HPLC) and CBC results achieved over the past 6 months were reviewed. Based on HPLC reports, patients were categorised into BTT and non-BTT groups, with each group comprising 25 age- and sex-matched patients. Discriminator indices, including Mentzer's Index (MI), Green and King Index (GKI), Sehgal Index (SI), Shine and Lal Index (SLI), Srivastava Index (SrI), and England and Fraser Index (EFI), were calculated for both groups. Statistical analysis was performed respective to standard cut-off values to establish new optimal cut-off values with the highest sensitivity and specificity.

Results: According to the results, SrI emerged as the best index, offering high sensitivity, specificity, Youden's Index, accuracy, and odds ratio. On the other side, SLI and GKI were observed to be poor indices with low sensitivity and specificity. The new optimal cut-off values for the best performance of each DI for BTT screening were as follows: SrI ≤3.5, MI ≤11.4, GKI ≤59.7, SI ≤709.4, SLI ≤941.1, and EFI ≤1.91.

Conclusion: The performance of DIs at standard cut-off values was poor to screen BTT. New optimal cut-off values provided maximal sensitivity and specificity thereby enhancing their performance as screening parameters for BTT in regions with a high-prevalence of the condition. Further studies are warranted to substantiate the new cut-off values for BTT screening.

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Introduction

β-thalassemia is an inherited quantitative haemoglobin (Hb) disorder caused by mutations in the β-globin gene (1,2). Patients with β-thalassemia trait (BTT), the heterozygous form, carry one abnormal and one normal β-globin gene, leading to mild anaemia (3). On High-Performance Liquid Chromatography (HPLC), healthy adults show normal HbA (~97%), HbA2 (~1.5-3.5%), and HbF (<0.8%) (4) while BTT patients show elevated HbA2 (~3.5-7%), reduced HbA, and normal HbF (3).

Screening for BTT and differentiating it from other causes of anaemia plays a significant role in preventing from the birth of patients with complex haemoglobinopathies (5). In developing nations where financial hardships may greatly compromise management protocols, cost-effective robust screening can significantly cut down the cost of unnecessary testing (6-8).

Discriminator indices (DIs), such as Mentzer's Index (MI), Green and King Index (GKI), Sehgal Index (SI), Shine and Lal Index (SLI), Srivastava Index (SrI), and England and Fraser Index (EFI) are commonly used to screen for BTT (9). Although numerous studies have highlighted the significance of these indices using standard cut-off values, there is no consensus on their usefulness (10-12). In this study, we evaluated standard and newly established optimal cut-off values for DIs to maximise their performance in BTT screening. This is the first study that recommends the use of new cut-off values for DIs to enhance their sensitivity and applicability.

Methods

This was a retrospective observational study. All procedures were in accordance with the standard ethical guidelines under the 1975 Helsinki Declaration and its 2008 revision. All national and international guidelines of good laboratory practice were implemented. No medical interventions were executed, and no living tissues were used in this study.

The retrospective study was approved by the institutional ethics committee, in which data acquisition was only for clinical and research purposes. All the procedures performed were parts of the routine patient care. All data collected and analysed were taken from hospital archives. No human tissue was used, and no intervention or modification was done in treatment protocols.

Recruitment of cases: Out of 2,40,109 complete blood counts (CBC) performed between November 2022 and April 2023, 72 requests were received for haemoglobinopathy work-up by HPLC as a part of anaemia screening.

According to HPLC results, patients with HbA_2 between 3.5% and 7% were labelled as BTT, and others were labelled as non-BTT. Twenty-five age- and sex-matched patients were included in each group. Prior to testing for haemoglobinopathies, iron deficiency anaemia (IDA) was not ruled out due to financial constraints. In developing nations, like ours, the cost of biochemical testing for IDA is about 10 times the cost of performing HPLC. In the non-BTT group, work-up for IDA was performed only in 16 patients, 14 of whom were found to be iron deficient. Biochemical investigations for IDA were not performed in the remaining cases.

Complete blood counts were carried out on Sysmex XN-1000 Haematology Analyser, and HPLC was performed on BioRad D-10 Haemoglobin Testing System (Dual HbA_2/F/A1c program).

Exclusion criteria: In this study, the following cases were excluded:

1. Paediatric patients
2. Patients with massive blood loss during the last 120 days
3. Patients who had received blood transfusions during the last 120 days
4. Patients with abnormal total leucocyte and platelet counts

Discriminator indices were calculated as follows:

- MI = MCV/RBC (≤ 13 is suggestive of BTT) (9)
- GKI = (MCV^2 x RDW)/ (haemoglobin x 100) (≤ 65 is suggestive of BTT) (9)
- SI = MCV^2/RBC (≤ 972 is suggestive of BTT) (13)
- SLI = MCV^2 x MCH x 0.01 (≤ 1530 is suggestive of BTT) (9)
- SrI = MCH/RBC (≤ 3.8 is suggestive of BTT) (14)
- EFI = MCV-(5 haemoglobin)-RBC-3.4 (≤ 0 is suggestive of BTT) (14)

Statistical analyses: Mean ± standard deviation with 95% confidence interval (Mean ± SD, 95% CI) and coefficient of variation (CV%) were calculated. The Kolmogorov-Smirnov test was used to determine variables' distribution, which showed no deviation from normally distributed data. The test for statistical significance included the independent sample two-tailed t-test, and *p*-value of ≤0.05 was considered statistically significant. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, Youden's Index (YI), and odds ratio (OR) were calculated. Sensitivity is the true positive rate and gives the probability of a positive test result when the patient has the disease. Specificity is the true negative rate and gives the probability of a negative test when the patient does not have the disease. Also, PPV and NPV reflect the percentage of positive and negative test results that represent true positive and

negative cases and indicate the probability of having or not having a disease when the test result is positive or negative. The accuracy of the test is its potential to detect the presence or absence of a disease, and YI gives the maximum potential effectiveness of a biomarker based on the highest sensitivity and specificity to obtain an appropriate cut-off point. Finally, OR reflects the association between the exposure and outcome and represents the odds of the occurrence of a disease when the test shows a positive result. An OR> 1 shows a positive correlation between the test result and the disease, while an OR< 1 shows a negative correlation.

Receiver operating curve (ROC) was generated, and area under curve (AUC) was obtained. The ROC is a graphical representation of the performance of a test, according to which AUC is calculated. The AUC ranges from 0 to 1, and a greater value of AUC reflects a better test performance.

Results

This study included 25 BTT and 25 non-BTT subjects.

Haematological parameters among BTT and non-BTT cases have been shown in Table 1. RBC count and RDW were higher among BTT cases, while haemoglobin, MCV, MCH, and MCHC were higher among non-BTT individuals. This difference was statistically significant for MCV, MCH, MCHC, and RDW but was not statistically significant for RBC count and haemoglobin.

Comparison of DIs among BTT and non-BTT *cases* showed that according to the median and quartiles of DIs, as shown on box plots in Figure 1(a-f), MI, SI, SLI, and SrI showed outliers among BTT cases, while GKI and EFI showed outliers among non-BTT individuals.

Table 2 displays the mean ± SD along with CV% of the DIs. The means of MI, SI, and SLI were lower while the means of GKI and EFI were higher than respective cut-off values in both groups. Mean SrI was lower than the cut-off value among BTT cases and higher than the cut-off value among non-BTT cases. The difference in these values between the two groups was statistically significant for all indices except for GKI.

Statistical analyses for comparison of the performance of DIs in BTT screening have been shown in Table 3. Sensitivity and specificity signify true positive and true negative cases, respectively (15,16). An ideal index will have high sensitivity and specificity. In this study, sensitivity was the highest for MI, and specificity was the highest for EFI (Figure 2(a-f)).

Predictive values reflect the probability of a disease with respect to the positive/negative index. A high PPV signifies a high probability that a positive index will predict having BTT, while a high NPV signifies a high probability that a negative index will foretell not having BTT (13,17). An ideal index will have high PPV and NPV. In this study, NPV was the highest for MI and GKI, and PPV was the highest for EFI (Table 3).

The accuracy of an index is the proportion of true positive and true negative cases respective to all evaluated cases (14,18). In this study, EFI had the highest accuracy while SLI attained the lowest (Table 3).

The YI defines the maximum potential effectiveness at a particular cut-off value (19,20). In this study, SrI had the highest YI while SLI obtained the lowest (Table 3).

Finally, OR indicates the association between an index and a disease. An OR> 1 mirrors a higher odd of a disease, while OR< 1 represents a lower odd (21). The OR was the highest for MI and the lowest for GKI. According to *p* values, observations were statistically significant for SC, MI, SI, SrI, and EFI and statistically insignificant for GKI and SLI (Table 3).

ROC curve analysis and AUC values evaluate the performance of a test by assessing its sensitivity and specificity at varying cut-off values (22,23). The AUC value varies from 0 to 1 (15). The ROC curves of the DIs in this study are shown in Figure 3(a-f), and AUCs are summarized in Table 3. Among DIs, the SI had the highest AUC while GKI had the lowest AUC. Using ROC curve analysis, the sensitivity and specificity of the DIs at varying cut-off values were calculated (Table 4).

Table 1. Haematological parameters among β-thalassemia trait and non-β-thalassemia trait cases

Haematological parameters	β-thalassemia trait		Non- β-thalassemia trait		P-value
	Mean ± SD (95%CI)	CV%	Mean ± SD (95%CI)	CV%	
Red blood cell count (x10^6/µL)	6 ± 0.8 (5.69-6.31)	13.5	5.6 ± 0.6 (5.36-5.83)	11.0	0.065
Haemoglobin (g/dL)	10.2 ± 1.5 (9.61-10.8)	15.0	10.5 ± 1.4 (9.95-11.0)	14.0	0.496
Mean corpuscular volume (fL)	61.5 ± 7.6 (58.5-64.5)	12.5	71.1 ± 6.7 (68.5-73.7)	9.6	< 0.001
Mean corpuscular haemoglobin (pg)	19.2 ± 4.3 (17.5-20.9)	23.0	23.4 ± 4.1 (21.8-25)	17.7	0.001
Mean corpuscular haemoglobin concentration (g/dL)	29.9 ± 1.3 (29.4-30.4)	4.31	31.4 ± 1.9 (30.7-32.1)	6.1	0.002
Red cell distribution width (%)	18.2 ± 2.9 (17.1-19.3)	16.4	15.0 ± 2.1 (14.6-16.2)	14.1	< 0.001

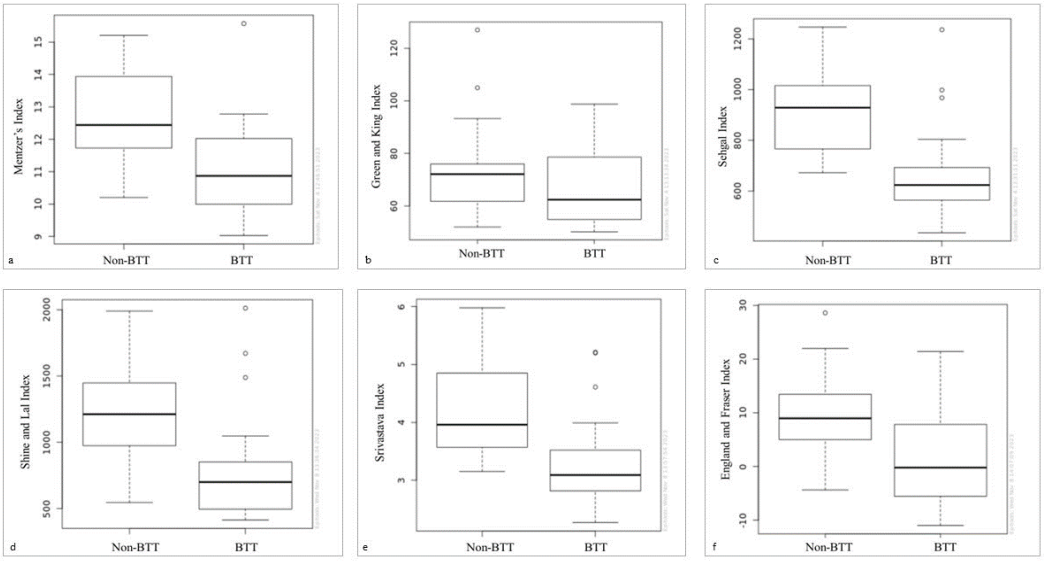

Figure 1. Box plots for discriminator indices among non-β-thalassemia trait (non-BTT) and β-thalassemia trait (BTT) cases. (a) MI, (b) GKI, (c) SI, (d) SLI, (e) SrI, (f) EFI

Table 2. Discriminator indices among β-thalassemia trait and non- β-thalassemia trait cases

Discriminator indices	Cut-off value	β-thalassemia trait		Non- β-thalassemia trait		P-value
		Mean ± SD (95%CI)	CV%	Mean ± SD (95%CI)	CV%	
Mentzer index	≤13	10.5 ± 1.8 (9.79-11.2)	17.2	12.8 ± 1.4 (12.3-13.3)	11.1	0.00001
Green and King index	≤65	67.7 ± 14.8 (61.9-73.5)	22.3	72.9 ± 16.7 (66.35-79.45)	23.3	0.263
Sehgal index	≤972	652.8 ± 183.0 (581.0-725.0)	28.61	916.6 ± 158.7 (854.0-979.0)	17.6	0.00001
Shine and Lal index	≤1530	774.19 ± 392.74 (620.2-928.1)	5.77	1213.52 ± 368.37 (1069.1-1358.1)	30.98	0.00022
Srivastava index	≤3.8	3.27 ± 0.77 (2.96-3.57)	24.01	4.23 ± 0.84 (3.90-4.55)	20.22	0.00138
England and Fraser index	≤0	1.01 ± 9.34 (-2.65-4.671)	944.01	9.51 ± 7.52 (6.56-12.46)	80.87	0.0011

Table 3. Statistical analysis for comparison of discriminator indices for screening of β-thalassemia trait

Comparative parameters	Mentzer's index	Green and King index	Sehgal Index	Shine and Lal index	Srivastava index	England and Fraser index
Sensitivity (%) (95%CI)	96.0 (79.65-99.90)	56.0 (34.93-75.60)	92.0 (73.97-99.02)	92.0 (73.97-99.02)	84.0 (63.92-95.46)	52.0 (31.32-72.20)
Specificity (%) (95%CI)	44.0 (32.89-3.05)	64.0 (42.52-82.03)	36.0 (17.97-57.48)	24.0 (9.36-45.13)	64.0 (42.52-82.03)	92.0 (73.97-99.02)
Positive Predictive Value (%) (95%CI)	2.5 (2.06-3.60)	2.3 (1.25-4.25)	2.1 (1.57-2.91)	1.8 (1.42-2.31)	3.43 (2.01-5.80)	9.0 (2.43-28.27)
Negative Predictive Value (%) (95%CI)	99.80 (99.12-99.98)	98.80 (98.25-99.39)	99.60 (98.61-99.92)	99.49 (97.77-99.89)	99.60 (99.03-99.85)	99.21 (98.8- 99.48)
Accuracy (%) (95%CI)	70.0 (36.51-60.72)	60.0 (49.07-76.98)	64.0 (23.64-51.66)	25.0 (13.86-39.28)	64.30 (49.50-77.34)	91.40 (79.98-97.46)
Youden's Index (%)	40.0	20.0	28.0	16.0	48.0	44.0
Odd's Ratio (95% CI)	18.85 (2.19-161.9)	2.26 (0.72-7.04)	6.46 (1.23-34.01)	3.63 (0.65-20.11)	9.33 (2.43-35.83)	12.45 (2.40-64.49)
P-value	0.0074	0.1589	0.0275	0.1398	0.0011	0.0026
Area Under Curve (95%CI)	0.842 (0.727-0.958)	0.585 (0.418-0.752)	0.877 (0.766-0.987)	0.807 (0.673-0.940)	0.815 (0.690-0.940)	0.744 (0.600-0.889)

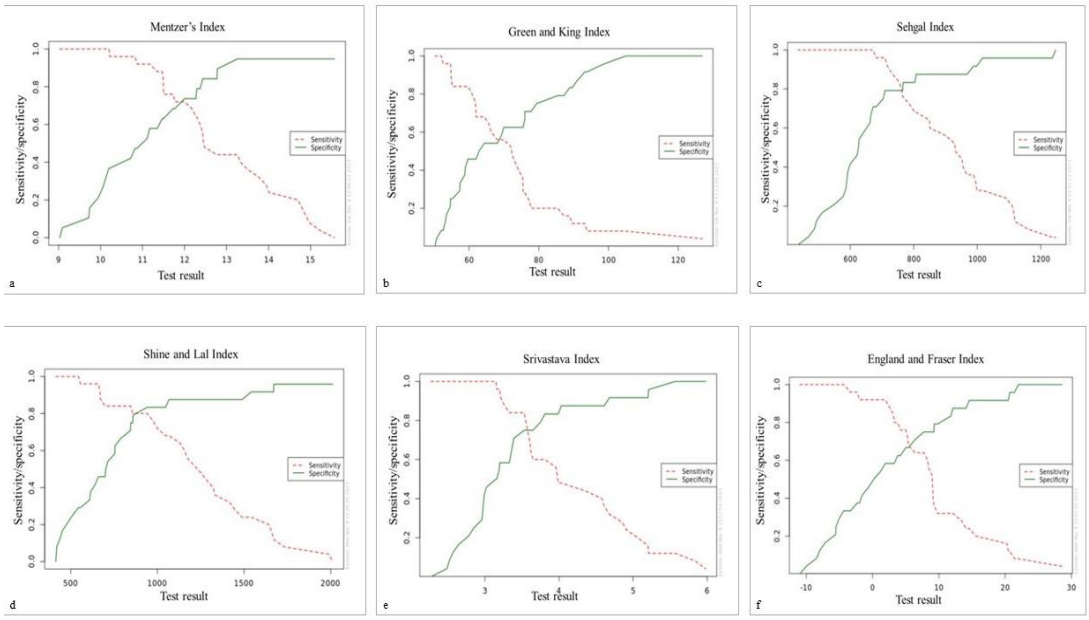

Figure 2. Sensitivity/specificity graphs for discriminator indices for the screening of β-thalassemia trait. (a) MI; sensitivity =96.0%, specificity=44.0%. (b) GKI; sensitivity=56.0%, specificity=64.0%. (c) SI; sensitivity=92.0%, specificity=36.0%. (d) SLI; sensitivity=92.0%, specificity=24.0% (e) SrI; sensitivity=84.0%, specificity=64.0%. (f) EFI; sensitivity=52.0%, specificity=92.0%

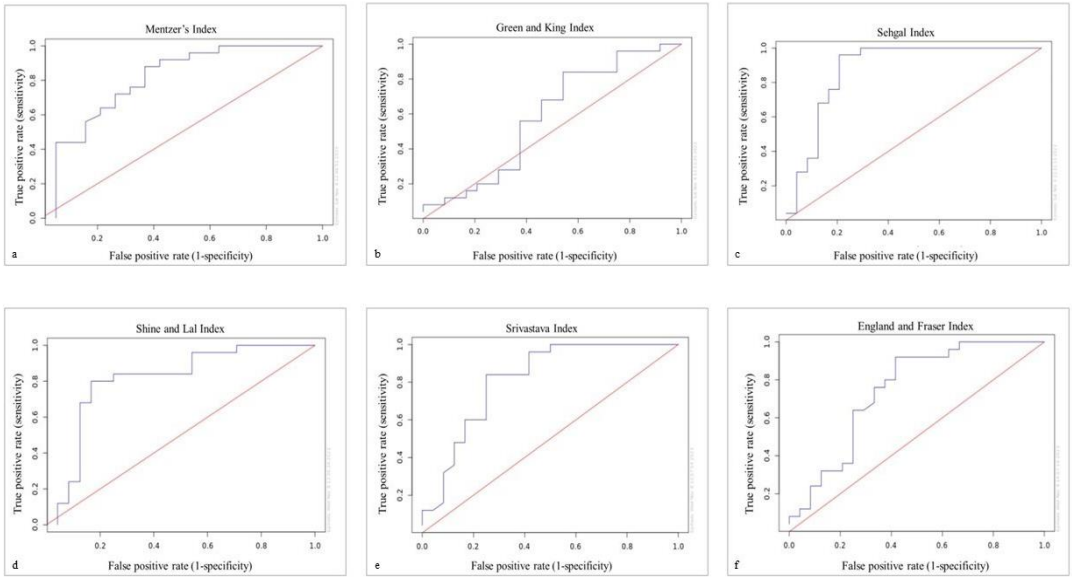

Figure 3. Receiver operating curve showing area under curve. (a) MI; AUC=0.842. (b) GKI; AUC=0.585. (c) SI; AUC=0.877. (d) SLI; AUC=0.807 (e) SrI; AUC=0.815. (f) EFI; AUC=0.744

Table 4. Sensitivity and specificity of discriminator indices at varying cut-off values for the screening of β-thalassemia trait

Discriminator indices	Cut–off values	Sensitivity (%)	Specificity (%)
Mentzer's index	≤ 11.2	92.0	66.7
	≤ 11.4	88.0	70.8
	≤ 13	96.0	44.0
	≤ 13.2	44.0	95.8
Green and King index	≤ 54.7	96.0	25.0
	≤ 59.7	84.0	45.8
	≤ 60.8	80.0	45.8
	≤ 65	56.0	64.0
	≤ 88.8	16.0	83.3
Sehgal index	≤ 709.40	96.0	79.2
	≤ 762.2	80.0	79.2
	≤ 972	92.0	36.0
	≤ 987.8	36.0	91.7
Shine and Lal index	≤ 668.87	92.0	45.8
	≤ 941.19	80.0	83.3
	≤ 1530	92.0	24.0
	≤ 1542.11	24.0	91.7
Srivastava index	≤ 3.21	92.0	58.3
	≤ 3.53	80.0	75.0
	≤ 3.8	84.0	64.0
	≤ 4.68	32.0	91.7
England and Fraser index	≤ -2.32	96.0	37.5
	≤ 0	52.0	92.0
	≤ 1.91	92.0	58.3
	≤ 3.78	80.0	62.5

Discussion

β-thalassemia is common in the Mediterranean region, the Middle East, and Southeast Asia. The worldwide prevalence of BTT is 1.5%, but it is more prevalent in some regions. In India, for example, the prevalence of this condition reaches 1.25-1.66% (10). Various researchers have studied the utility of DIs in screening for BTT; a few recent studies have been shown in Table 5 (24,25).

Traditionally, RBC count ≥5 x10^6/μL and MCV ≤70 fL suggest to further proceed with a haemoglobinopathy work-up (3). In this study, the mean RBC count was higher than ≥5 x10^6/μL among both groups (Table 1); however, this difference between the two groups was not statistically significant. The mean MCV was ≤70 fL among BTT cases and >70 fL in the non-BTT group. This difference was statistically significant. Bhargava *et al.* reported similar results (9). Further, RDW was significantly higher among BTT than non-BTT cases. This was an unexpected finding in this study and could be due to the fact that non-BTT cases might have had varying causes of anaemia with variable RDW. Iron deficiency anaemia was confirmed only in 14 cases in the non-BTT group. In the remaining 11 cases, the cause of anaemia was under evaluation, but limited testing was performed due to financial constraints.

In this study, SrI emerged as the best index with a high sensitivity, NPV, and specificity, as well as the highest YI. Also, the OR of this index was high and statistically significant (Table 3). This signified high true positive and negative rate, meaning a high probability that a negative index would predict not having BTT and higher odds of having BTT with a positive index. The mean SrI value was lower than the cut-off among BTT cases and higher than the cut-off among non-BTT cases, an observation that was statistically significant (Table 2). The optimal cut-off of ≤3.5 increased the specificity while sensitivity remained unchanged (Table 4). Similarly, a study by Singh et al. found that SrI was the best index (Table 5) (26).

Two other indices, MI and SI, showed comparable performance, with both having high sensitivity and NPV but low specificity and YI (Table 3). The OR was the highest for MI and statistically significant for both indices. These analyses signified that both indices had high true positive rates, indicating a high

probability that a negative index would predict not having BTT but higher odds of having BTT for cases with a positive index. The rate of true negative was low, and SI claimed the highest AUC (Table 3). The mean MI and SI values were lower than the cut-off values in both groups, but the difference between the two groups was statistically significant (Table 2), implying that the standard cut-off value was high, requiring a lower cut-off value to correctly categorize individuals. The optimal cut-off value of ≤11.4 for MI decreased sensitivity but increased specificity (Table 4), making MI a superior screening tool. The optimal cut-off value for SI was set at ≤709.4, which increased its sensitivity and specificity. Bhargava et al., Rastogi et al., and Singh et al. found MI and SI were good indices (9,25,26), and Rastogi et al. found SI to be the best index (Table 5) (25).

Table 5. Discriminator indices in various studies (Reference numbers in parenthesis)

Discriminator index	Study	Sensitivity (%)	Specificity (%)	Youden's Index (%)
Mentzer's index	Surjawan et al, 2017 (24)	79.0	83.0	-
	Jahangiri et al, 2017 (14)	89.1	78.6	67.6
	Rastogi et al, 2020 (25)	88.4	97	85.4
	Bhargava et al, 2020 (9)	80.6	88.7	69.3
	Singh et al, 2023 (26)	50	99	49
	Surjawan et al, 2017 (24)Error! Bookmark not defined.	90.0	92.0	-
	Jahangiri et al, 2019 (14)	86.5	78.6	65.2
	Rastogi et al, 2020 (25)	70.5	97.9	68.4
	Bhargava et al, 2020 (9)	78.5	94.1	72.58
	Singh et al, 2020 (10)	67.1	-	43.9
	Singh et al, 2023 (26)	50.0	99.0	49.0
Sehgal index	Jahangiri et al, 2019 (14)	96.0	64.5	60.6
	Bhargava et al, 2020 (9)	77.5	87.3	64.9
	Surjawan et al, 2017 (24)	55.0	56.0	-
	Jahangiri et al, 2019 (14)	100.0	17.5	17.5
	Singh, 2020 (10)	-	91.1	-
	Rastogi et al, 2020 (25)	91.0	96.8	87.8
	Bhargava et al, 2020 (9)	100	3.54	32.0
	Singh et al, 2023 (26)	80.0	85.0	65.0
Srivastava index	Jahangiri et al, 2019 (14)	74.8	80.8	55.67
	Bhargava et al, 2020 (9)	34.6	97.3	32.0
	Singh et al, 2023 (26)	40.0	98.0	38.0
England and Fraser index	Jahangiri et al, 2019 (14)	62.9	85.4	48.3
	Singh et al, 2020 (10)	64.0	-	40.7
	Reis et al, 2020 (27)	75.0	92.0	-
	Bhargava et al, 2020 (9)	77.5	91.0	68.5
	Singh et al, 2023 (26)	30	100	30

Among indices, GKI emerged as an index with poor performance and low sensitivity, specificity, and YI (Table 3). Its OR and AUC were the lowest in this study and statistically insignificant (Table 3). The mean GKI was higher than the cut-off value in both groups, and the difference between the two groups was not statistically significant (Table 2). The optimal cut-off value was obtained as ≤59.7 to increase the sensitivity at the cost of a decrease in specificity (Table 4). Bhargava *et al*. and Sehgal *et al*. found GKI to be the best-performing index (Table 5) (9,13).

We also observed SLI to be a poor screening index. Although this index had high sensitivity and NPV, but it delivered the lowest specificity, PPV, accuracy, and YI (Table 3). Also, its OR was low and statistically insignificant. The mean SLI was lower than the cut-off in both groups, but the difference was statistically significant (Table 2), implying that the standard cut-off was high, requiring the setting of a lower cut-off to separate cases. The optimal cut-off value of ≤941.1 remarkably decreased the sensitivity and increased the specificity of this index (Table 4). In contrast to this study, Bhargava et al., Singh V et al., and Singh N et al. found the SLI to be a good-performing index (9,10,26), and Singh et al. found SLI to be the most specific for BTT (Table 5) (10).

Compared to the other indices, EFI yielded different results, obtaining the highest specificity and PPV but low sensitivity and YI (Table 3). The OR was high and statistically significant, signifying high true negative cases and the probability that a positive index would predict a high likelihood of BTT. These statistical characteristics made EFI a poor screening index, instead sliding it more towards the qualities of a diagnostic test. The mean EFI was higher than the cut-off in both groups (Table 2), reflecting that the standard cut-off value was low and needed to be higher to correctly classify cases. The optimal cut-off value of ≤1.91 boosted the sensitivity but decreased the specificity (Table 4), improving the qualities of the index as a screening tool. In contrast to our study, Reis et al. found that EFI performed better than other indices (27), and Singh et al. reported EFI to be the best index (Table 5) (26).

This study had a small sample size, and the data were collected from a single centre catering to a geographic region where BTT was common. Larger multi-centric studies can obviate these limitations. Due to financial constraints, biochemical investigations for IDA were not done for all patients, a condition that can affect the level of HbA_2. Incorporating biochemical analyses and HPLC would greatly help refine this study's results.

Conclusion

Discriminator indices are helpful for BTT screening, and new optimal cut-off values for these indices can improve their performance. In this study, SrI was emerged as the best index with high sensitivity, specificity, YI, accuracy, and OR at the standard cut-off of ≤3.8. The optimal cut-off for SrI was ≤3.5. The MI had the highest sensitivity and OR but low specificity, which could be improved by changing the standard cut-off from ≤13 to the optimal cut-off of ≤11.4. The SI had high sensitivity and OR, but its specificity was low, which was improvable by changing the standard cut-off from ≤972 to the optimal cut-off of ≤709.4. The GKI and SLI were poor indices. GKI had low sensitivity, specificity, YI, and OR, while SLI had the lowest specificity, accuracy, and YI. The GKI performance was improved slightly after altering its standard cut-off from ≤65 to the optimal cut-off of ≤59.7. The SLI could also be improved by changing its standard cut-off from ≤1530 to the optimal cut-off of ≤941.1. Finally, the EFI was the most specific and accurate for BTT, but its sensitivity was low. Changing the standard cut-off of 0 to the optimal cut-off of ≤1.91 improve the performance of EFI as a screening tool. Larger studies are required to validate these new optimal cut-off values and enhance their applicability in BTT management.

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Ethical statement

All procedures in this study were in accordance with the standard ethical practices under the institutional, national, and international guidelines under the Helsinki Declaration, 1975, and its revision in 2008. This research was conducted retrospectively based on the data obtained for clinical purposes. All the procedures performed were parts of the routine patient care. Consent was obtained as a part of hospital procedures when the patient was admitted to the hospital. No medical interventions or living tissues were used in this study. Approval for access to archived data was obtained from the Institutional Ethics Committee.

Conflicts of interest

The authors declare that they have no financial or non-financial interests.

Author contributions

AH: Conceptualisation; VVAM: Ethical approval; JC, RC: Data Collection; KK, AP: Data compilation and statistical analyses; AH: Manuscript writing; VVAM: Manuscript editing

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