Performance analysis of machine learning algorithms and screening formulae for β–thalassemia trait screening of Indian antenatal women

Das, Reena; Saleh, Sarkaft; Nielsen, Izabela; Kaviraj, Anilava; Sharma, Prashant; Dey, Kartick; Saha, Subrata

Published in:
International Journal of Medical Informatics

DOI (link to publication from Publisher):
10.1016/j.ijmedinf.2022.104866

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

International Journal of Medical Informatics 167 (2022) 104866

Contents lists available at ScienceDirect

International Journal of Medical Informatics

journal homepage: www.elsevier.com/locate/ijmedinf

Performance analysis of machine learning algorithms and screening formulae for β–thalassemia trait screening of Indian antenatal women

Reena Das [a], Sarkaft Saleh [b], Izabela Nielsen [b], Anilava Kaviraj [c], Prashant Sharma [a], Kartick Dey [d], Subrata Saha [b]

[a] Department of Hematology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India
[b] Department of Materials and Production, Aalborg University, DK 9220 Aalborg, Denmark
[c] Department of Zoology, University of Kalyani, Kalyani 741235, India
[d] Department of Mathematics, University of Engineering & Management, Kolkata 700160, India

ARTICLE INFO

Keywords:
β-Thalassemia carrier screening
Supervised machine learning algorithm
Multi-criteria decision-making
Antenatal Women
Diagnostic performance

ABSTRACT

Background: Currently, more than forty discrimination formulae based on red blood cell (RBC) parameters and some supervised machine learning algorithms (MLAs) have been recommended for β-thalassemia trait (BTT) screening. The present study was aimed to evaluate and compare the performance of 26 such formulae and 13 MLAs on antenatal woman data with a recently developed formula SCS_{BTT}, which is available for evaluation in over seventy countries as an Android app, called *SUSOKA* [16].

Methods: A diagnostic database of 2942 antenatal females were collected from PGIMER, Chandigarh, India and was used for this analysis. The data set consists of hypochromic microcytic anemia, BTT, Hemoglobin E trait, double heterozygote for Hemoglobin S and BTT, heterozygote for Hemoglobin D Punjab and normal subjects. Performance of the formulae and the MLAs were assessed by Sensitivity, Specificity, Youden's Index, and AUC-ROC measures. A final recommendation was made from the ranking obtained through two Multiple Criteria Decision-Making (MCDM) techniques, namely, Simultaneous Evaluation of Criteria and Alternatives (SECA) and TOPSIS.

Results: It was observed that Extreme Learning Machine (ELM) and Gradient Boosting Classifier (GBC) showed maximum Youden's index and AUC-ROC measures compared to all discriminating formulae. Sensitivity remains maximum for SCS_{BTT}. K-means clustering and the ranking from MCDM methods show that SCS_{BTT}, Shine & Lal and Ravanbakhsh-F4 formula ensures higher performance among all formulae. The discriminant power of some MLAs and formulae was found considerably lower than that reported in original studies.

Conclusion: Comparative information on MLAs can aid researchers in developing new discriminating formulae that simultaneously ensure higher sensitivity and specificity. More multi-centric verification of the formulae on heterogeneous data is indispensable. SCS_{BTT} and Shine & Lal formula, and ELM and GBC are recommended for screening BTT based on MCDM. SCS_{BTT} can be used with certainty as a tangible cost-saving screening tool for mass screening for antenatal women in India and other countries.

1. Introduction

Hemoglobinopathies are a group of inherited hemoglobin (Hb) disorders with abnormal production or structure of the globin polypeptide chain(s). According to the World Health Organization (WHO), approximately 5% of the world population are carriers of Hemoglobinopathies and prevalence of anemia in antenatal women is alarmingly high (> 40%) mostly in low-and middle-income countries[1]. The common causes of anemia include deficiencies of iron, vitamin B12 and folate; and are reasons for estimated 273,000 annual deaths [12].

Iron deficiency anemia (IDA) can be considered an acquired disorder and can be treated with iron therapy. However, thalassemia is an inherited genetic disease and needs early identification and prognosis as the carriers can transmit their defective gene to the next generation. It is essential to differentiate between IDA and β-thalassemia traits (BTT) to advise partners in screening for BTT and unnecessary use of iron therapy. However, discrimination of BTTs by RBC parameters is always a challenge in countries where anemia syndromes are concurrently

[1] www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-anaemia-in-women-of-reproductive-age-(-)

https://doi.org/10.1016/j.ijmedinf.2022.104866
Received 3 June 2022; Received in revised form 19 July 2022; Accepted 7 September 2022
Available online 16 September 2022

prevalent. Definitive methods for differential diagnosis between carriers and IDA include quantitative detection of Hemoglobin A2 (HbA2) and DNA studies. But these are expensive and time-consuming for mass screening. Moreover, availability and accessibility of such differential diagnostic tests are limited in low-resource countries. It leads to a substantial challenge to develop an inexpensive, easily accessible, and interpretable screening formula. A cost-effective, evidence-based carrier screening formula can reduce significant healthcare burden, increase the efficiency of resource utilization, and, most importantly, early intervention can reduce the burden of these disorders.

This study evaluates the performance of formulae and MLAs on hematological data of Indian antenatal females, where β-thalassemia is prevalent across the country (3–4%) along with other symptomatic hemoglobinopathies like HbS, HbE, and asymptomatic hemoglobin disorders like HbQ, and HbD Punjab or Iran. According to a 2016 medical report published by the Ministry of Health & Family welfare[2], Government of India, the number of thalassemia major is near about 1.5 lakhs and the number of β-thalassemia carriers is almost 42 million. In certain communities, such as Sindhis, Punjabis, Gujaratis, Bengalis, Kolis, Saraswats, Lohanas and Gaurs, an unexpected higher frequency (approximately 40%) are reported. In India, approximately 10,000–15,000 babies are born with thalassemia major and has the largest number of thalassemia major children in the world. Offering a DNA test analysis for all subjects to detect causative mutation can lead to a substantial healthcare burden for the government. The definitive treatment available for these children is bone marrow transplantation (BMT). However, the existing facilities of BMT can support only a few children because of the prohibitive cost, paucity of BMT centers, or non-availability of a suitable Human Leukocyte Antigens (HLA) matched donor. The estimated 40-year lifespan cost of treating a patient is $97,500, and early identification can save such cost and expedite clinical workflow.

Over the last couple of decades, various mathematical formulae based on RBC parameters have been recommended, and over forty such formulae are presently available. Noticeably, in these formulae' specificity or sensitivity measures varied considerably under independent validation. [12]. These discrepancies could be associated with analytical factors for a model development methodology, limited data sources, regional differences, demographic characteristics, and others. Recently, some researchers recommended the use of machine learning algorithms (MLAs) instead of the formulae [24,41]. We present a brief overview of the present state-of-art (mainly after 2000) of screening BTT by formulae and MLAs in Table 1 and subsequent recommendation across the world.

Table 1 indicates that some authors preferred MLAs and overlooked the comparative evaluation of the available formulae [2,47] while others emphasized only on formulae [26,80]. Additionally, many authors used the data set with limited variants, excluding other possible variants (such as: HbE, HbS) that may affect the outcome [32,48] while implementing mass thalassemia screening program.

The performance measures used for screening tests have their unique merits and limitations. For example, sensitivity and specificity are often recommended to measure performance because they provide information on how well a dichotomous test can distinguish between diseased and non-diseased samples at a given cut-point threshold. Knowing the performance of a particular measure of a screening formula/algorithm used in clinical decision-making is paramount for clinicians. However, it is not necessary that a single formula or algorithm can ensure the highest measure for all performance indicators. Therefore, multi-criteria decision making (MCDM) can be a structural and practical approach for making a final recommendation. Weight for each criterion (performance indicator) directly influences the final ranking of the MCDM method, and those can be defined objectively or subjectively. However, subjective weights can be assigned based on the experiences of the experts, and objective weights can be used through mathematical calculations based on the structure of the data set. In this study, we use Simultaneous Evaluation of Criteria and Alternatives (SECA) and Technique for Order of Preference by Similarity to Ideal Solution (TOPSIS) to generate a final ranking based on all four performance indicators. TOPSIS, developed by Hwang and Yoon in 1981, is one of the simple MCDM ranking methods used extensively to solve real-world decision problems in diverse application areas [9,65]. We use a similar approach was used by Mishra et al. [53] while implementing the TOPSIS method. However, the SECA method is developed recently by Keshavarz-Ghorabaee et al. [39] and two key advantages of the method are: first, there is no need to weight the criteria separately, and second, the method can set weights for each criterion and generate final ranking by solving a multi-objective non-linear programming model. This method has also gained popularity in solving real-life conflicting decision-making problems quickly due to its easy application [19,4].

Earlier, we hybridized decision trees (DTs) and artificial neural network (ANN); and proposed screening formula SCS_{BTT} [16]. The critical hypothesis of that study was to strictly identify BTTs (with sensitivity as high as possible), even if a fraction of normal individuals or other variants were recommended for further evaluation (compromising with specificity). The objective was to ensure a tangible cost-saving tool for medical practitioners and other organizations so that most of the population could be competently excluded with certainty during a carrier screening program. Later, the formula was implemented in an android based application software, called 'SUSOKA', freely available in over seventy countries for blind evaluation. Despite several decades of research, the RBC-based discriminant formulae are yet to make the transition to routine clinical diagnostics. Further, the multitude of available formulae makes it difficult to choose between them based on the various performance measure to arrive at a diagnostic conclusion. This study aims to assess the diagnostic performance of a newly-designed web application-based screening strategy for diagnosing the BTTs and common hemoglobinopathies. We compared the 27 different discriminating formulae (including SCS_{BTT}) and 13 MLAs on data of antenatal subjects and made decisions about a referral through the MCDM theory. The objective is to provide practical guidance on using low-cost tests (e.g., complete blood count (CBC), which costs <$2) instead of using expensive confirmatory tests (such as HPLC, which costs $20–50 per test). Further, from the perspective of academic research, we aim to identify the premier MLAs that can be used to develop the BTT screening formula. Further, we conducted the trade-off analysis among various performance measures through MCDM approaches for selecting appropriate methods to screen the patients proven to have various inherited hemoglobinopathies.

2. Material and Methods

Population evaluated: The formula SCS_{BTT}, was developed from data set collected from the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh during 2016–2018 [16]. For the present study, we collected a new data set containing all active patient recruited during December 2019 to March 2022 from the Department of Hematology at PGIMER, Chandigarh, India, for valiadation of the formulae and the MLAs. Routine diagnoses for thalassemia and hemoglobinopathies are performed in this institute. The data set consisted of 2942 samples (513 IDA, 1663 normal individuals, 665 BTT, and 101 other hemoglobin variants). Out of 513 IDA samples: 184 had been diagnosed with "moderate anemia", 27 with "severe anemia", and the rest with "mild anemia". Out of the 665 BTT samples: 118 had concomitant IDA. Out of the 101 other variants: 74 had HbE trait, 22 had HbD Punjab trait, 2 had HbD Iran trait, 1 had HbQ India trait, 1 had Hb Fontainebleau and 1 had homozygous HbE. The hemogram laboratory at PGIMER is under the United Kingdom National External Quality Assessment Service (UK NEQAS) Hematology program, and

[2] http://nhm.gov.in/images/pdf/programmes/RBSK/Resource_Documents/Guidelines_on_Hemoglobinopathies_in%20India.pdf

Table 1
Related work on evaluating formulae and MLAs.

Formula	Location	Major variants	Methods	Data set	Best
[2]	Italy	α thalassemia, BTT, NS	SVM, KNN, MLP	Train and test set: 304	MLP
[56]	Greece	IDA, BTT	6 formulae	Test set: 493	G & K
[68]	China	IDA, BTT	12 formulae	Test set: 300	G & K, E&F Ricerca(RDWI)
[32]	France	IDA, BTT	11 formulae	Test set: 129	Green & King
[66]	Thailand	α thalassemia, BTT, HbE, Homozygous Hb E, NS	DT(C4.5), NB, MLP	Train set: 1402 Test set: 8054	MLP, NB
[47]	Italy	α thalassemia, BTT, NS	RBF, PNN, KNN	Train set: 196 Test set: 108	RBF
[7]	Israel	α thalassemia, BTT IDA, NS, MDS	ANN	Train and test set: 526	ANN
[78]	Spain	α thalassemia, BTT IDA, IDA-BTT	MDA	Train set: 480 Test set: 628	MDA
[26]	Taiwan	α thalassemia, BTT, IDA	10 formulae	Test set: 877	S & L
[49]	Brazil	α thalassemia, IDA, BTT	Fisher discriminant, ROC curve	Train set: 291 Test set: 227	Matos & Carvalho formula
[63]	Italy	BTT, NS	PLS-DA	Test set: 63	PLS-DA
[30]	Iran	IDA, BTT	DTs (QUEST, CHAID,CART, CRUISE,GUIDE, E-CHAID)	Train set: 144	CRUISE
[36]	Pakistan	α thalassemia, BTT, HbE, HbS, IDA	RF, DT(CART), 12 formulae	Train set: 428 Test set: 182	KF2
[1]	Palestine	BTT, NS	KNN, DT, NB, MLP	Train and test set: 45,498	MLP, NB
[42]	Thailand	BTT, IDA	KNN, DT, RF, ANN, SVM, 13 formulae	Train set: 186	KF2, SVM
[48]	Indonesia	BTT, IDA	Shine & Lal formula	Test set: 196	S & L
[16]	India	α thalassemia, BTT HbE, IDA	MLP, DT, RBF	Train set: 1076 Test set:492	SCS_{BTT}
[14]	Turkey	BTT, IDA	RELM, SVM, KNN, ELM, LR	Train set: 342	RELM
[24]	Spain	α thalassemia, BTT, IDA	ROC, 23 formulae	Test set: 2218	G & K, Jayabose
[29]	India	BTT, NS	DT(C4.5), ANN, NB	Train and test set: 420	ANN
[80]	Sri Lanka	IDA, BTT	11 formulae	Test set: 111	S & L
Present Study	India	IDA, BTT, HbE, NS	27 formulae, 13 MLAs	Test set: 2942	SCS_{BTT}, S & L, ELM, GBC

ANN, artificial neural network; CART, classification and regression trees; CHAID, CHi-squared automatic interaction detector; CRUISE, classification rule with unbiased interaction selection and estimation; DT, decision tree; E-CHAID, exhaustive CHAID; ELM, extreme learning machine; GUIDE, generalized, unbiased, interaction detection and estimation; KNN, k-nearest neighbor; LR, logistic regression; MDA, multiple discriminant analysis; MLA, machine learning algorithm; MLP, multi-layer perceptron; NB, naive bayes; PLS-DA, partial least square discriminant analysis; PNN, probabilistic neural network; QUEST, quick, unbiased, efficient statistical tree; RBF, radial basis function; RELM, regularized extreme learning machine; RF, random forest; ROC, receiver operating characteristic; SVM, support vector machine. MDS, myelodysplastic syndrome.

recommended controls as advised by the respective manufacturers are used. We refer to Fig. 1 for the overview of computational scheme used in this study.

Ethical consideration: Because only a retrospective evaluation of the automated red cell indices was carried out, the ethical clearance was not taken. No additional samples were taken, or tests were performed on the samples. All methods were performed following the relevant guidelines and the institution's regulations.

Diagnostic Performance: Based on the literature, 27 discrimination formulae and 13 MLAs were considered for evaluation (mostly from Table 1) by using measures such as $\text{Sensitivity(TPR)} = \frac{TP}{TP+FN}$; $\text{Specificity(TNR)} = \frac{TN}{TN+FP}$; $\text{Youden'sIndex(YI)} = TPR + TNR - 1$; $\text{AUC-ROC} = \frac{1}{2}\frac{FPR}{2} + \frac{TPR}{2} = \frac{1}{2} - \frac{FP}{2(FP+TN)} + \frac{TP}{2(TP+FN)}$, where TP, true positive; TN, true negative; FP, false positive; FN, false negative. If a formula or MLA had sensitivity, specificity, Youden's index, and AUC-ROC near to 1, it was considered a better differential performance.

Statistical analysis: *K*- means cluster and ANOVA were conducted where the significance level was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS-277 for Windows (IBM Corp, NY, USA).

Supervised learning models: This study compares 13 supervised MLAs: Random Forest (RF); Linear Support Vector Machine (SVM-L); Logistic Regression (LR); K-Nearest Neighbors (KNN); Decision Tree Classifier (DTC); Extra Trees Classifier (ETC); Bagging classifier (BC); Multi-layer Perceptron (MLP); Radial Basis Function kernel SVM (RBF-SVM); AdaBoost classifier(ADA); Linear Discriminant Analysis (LDA); Gradient Boosting for classification (GBC) and Extreme Learning Machine (ELM) were used for binary classifications and define a mapping between sample and output label. The data file was split into 70% training and 30% testing partitions using a defined seed value. Different seeds were chosen to maintain the training and testing set distributions. While applying the supervised learning algorithm, we used the following label: 1 = in favour of BTT and 0 = in favour of all other samples. An overview of the selected algorithms is presented in the Supplementary file. All MLAs were performed, and performance metrics were computed using the Python module Scikit-learn [60].

TOPSIS and SECA multi-criteria decision-making methods: We present the complete methodology for TOPSIS [5,55] and SECA [17,3] with explanation in the Supplementary file.

3. Results

In this study, we used five parameters: hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red blood cell (RBC), and red cell distribution width (RDW) of 2942 antenatal subjects. The Supplementary file shows the variation of these five parameters among four groups. The mean age was 27.6 years (standard deviation (SD)= 12.5). It was found that the mean and median values of MCV, MCH, and Hb were higher, and RDW and RBC were lower for the normal subjects (NS) compared to IDA, BTT, and other groups. The performance of the 27 formulae on the data set is presented in Table 2.

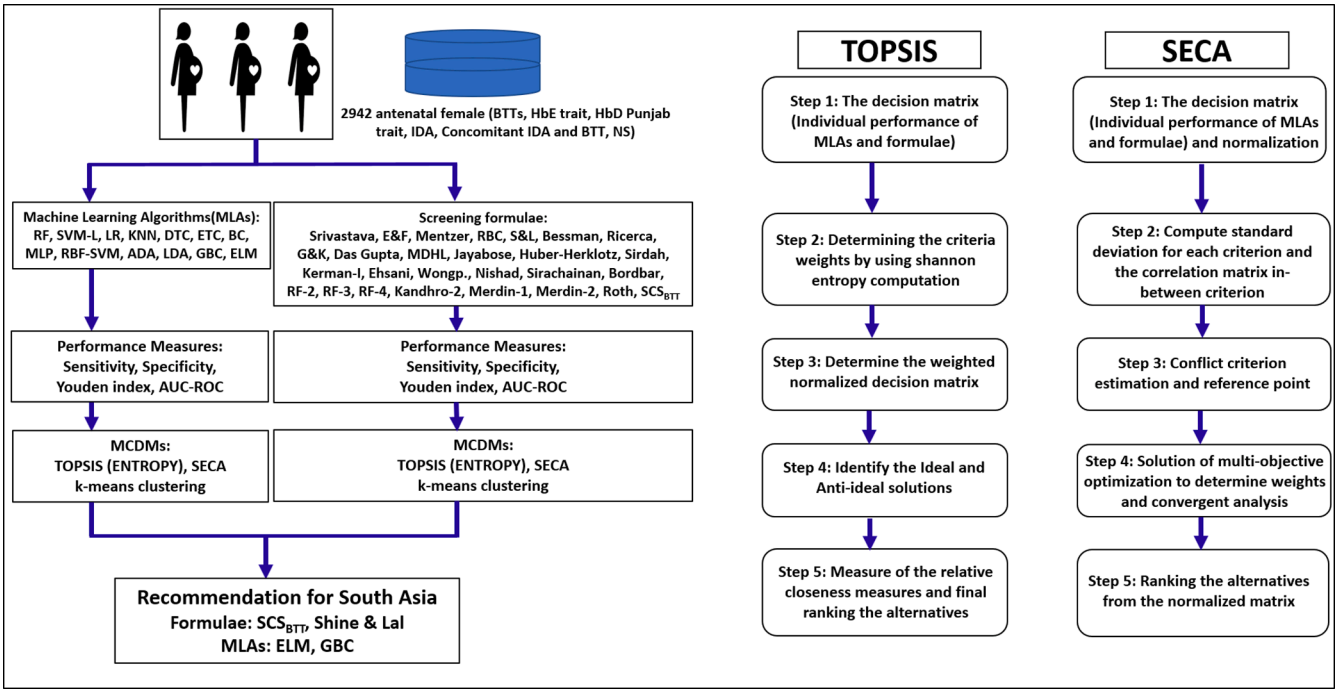

Fig. 1. Computational scheme for the study and MCDM methods.

We excluded some formulae such as *Index*26 [31] or *Janel*(11*T*) [32] as these authors used a combination of several formulae, which might be difficult to explain for clinicians. In addition, we excluded formula $M/Hratio = \frac{\%MicroR}{\%HypoHe}$ [77]; $MSI = \frac{\%MicroR}{MCV} \times MCHC \times Hb$ [12], because these formulae use parameters that required analyzers and methods that might not widely available in regions where healthcare resources are limited. It appears that the application of SCS$_{BTT}$ can ensure maximum sensitivity and is comparable with S&L formula and Ricerca formula (Table 2). However, the specificity of SCS$_{BTT}$ is low compared to many formulae (Table 2). S&L formula ensures the highest ROC-AUC and YI among all. SCS$_{BTT}$ and Ravanbakhsh-F4 remain comparable to each other in terms of YI and AUC-ROC. Next, we compared the performance of the 13 MLAs on the present data set, and the result is shown in Table 3.

From the perspective of MLAs, ELM and GBC demonstrate higher YI and AUC-ROC. Noticeably, all MLAs show higher specificity but lower sensitivity. Since the performance of formulae and MLAs varies considerably for each performance measure, we conducted K-mean clustering. The aim was to identify a subset of formulae and MLAs which ensure comparable performance with respect to all four measures (Fig. 2).

We conducted ANOVA for the cluster analysis (Table 2 in supplementary file), and the outcome shows that each measure makes a significant impact on deciding cluster members ($p < 0.05$). It is also observed from Fig. 2 that each performance measure varies considerably among the clusters. For example, Fig. (2b) demonstrates that Cluster-5 includes all those formulae (S&L, RF-4, and SCS$_{BTT}$) whose sensitivity, YI and AUC-RUC are relatively higher, whereas, Cluster-4 includes all those formulae (Bessman, Sirachainan, Huber-Herklotz) which showed comparatively lower performances. Note that while a high sensitivity and high specificity are preferable, however, usually there is a trade-off between sensitivity and specificity: as one increases, the other decreases [13,51]. Therefore, Cluster-5 includes all those formulae whose sensitivity is high compared to other algorithms without too much-sacrificing of the specificity measure. Similarly, Fig. (2 a) demonstrates that Cluster-2 includes all those MLAs (ADA, GBC, ELM, MLP) whose sensitivity, specificity, YI, and AUC-ROC are high. Overall, SCS$_{BTT}$, Sirdah, ELM and ELM & GBC show higher sensitivity, specificity, YI, AUC-ROC, respectively (Tables 2 and 3). However, the Sirdah formula does not appear in a good cluster because its specificity is too low, whereas Ravanbakhsh-F4 or ADA appears in good clusters because of relatively higher performance for all four measures.

Regarding the performance metrics to evaluate predictive screening methods, there is no unique guideline. Moreover, each measure has it own advantage and limitation [70]. For example, as stated by [73], *the Youden index is not a truly optimal decision rule for setting thresholds*. Therefore, MCDM methods are implemented and the final ranking is presented in the following Tables 4 and 5.

The results for the final ranking are consistent with the claim by Keshavarz-Ghorabaee et al. [39], Bahrami and Rastegar [6], where the author compares the outcome of the SECA method with other MCDM methods. Results reflect that the ranking for the two methods is almost similar and may further be used for final recommendation.

4. Discussion

A definitive diagnosis of BTTs should under ideal circumstances be performed by molecular genetic analysis. But one-third of the world population lacks access to essential health services, and has been continuously facing an extreme burden of health expenses of the costly methods of diagnosis (https://apps.who.int/iris/bitstream/handle/10665/311654/9789289054058-eng.pdf?sequence=1&isAllowed=y, accessed March 21, 2022). Noticeably, the cost of prevention through screening for BTTs is only one-tenth of the treatment costs [37, 22].

Therefore, early identification of BTT is the cornerstone of reducing the burden of thalassemia syndromes morbidity and mortality in most high-prevalence areas. The aim of using RBC-based formulae is to make early identification of BTT subjects to reduce unnecessary evaluation costs and resource utilization for large populations. It can significantly alleviate the burden of hemoglobinopathies on clinical services in middle and low-income countries [30]. However, RBC-based approaches suffer from interference of microcytosis and hypochromia, most notably iron deficiency, anemia of chronic disorders, and clinically much less relevant α-thalassemia trait/silent carrier state. The latter is less relevant in South Asia due to the prevalence of $\alpha +$ genotypes. The interference may also be caused by lead poisoning and vitamin C and E

Table 2
Performance analysis of discriminant formulae.

Study	Discriminating formula	Cut-off for BTT	Sens.	Spec.	YI	AUC-ROC
Srivastava [74]	$\frac{MCH}{RBC}$	<3.8	0.420	0.987	0.407	0.703
E&F [21]	$MCV - RBC - 5Hb$	<0	0.262	0.997	0.259	0.630
Mentzer [50]	$\frac{MCV}{RBC}$	<13	0.541	0.990	0.531	0.766
RBC [40]	RBC	> 5	0.580	0.950	0.531	0.765
S&L [69]	$\frac{MCV^2 \times MCH}{100}$	<1530	0.939	0.879	0.818	0.910
Bessman [10]	RDW	< 14	0.021	0.659	-0.320	0.340
Ricerca [62]	$\frac{RDW}{RBC}$	<4.4	0.905	0.198	0.103	0.552
G&K [23]	$\frac{MCV^2 \times RDW}{100Hb}$	<65	0.391	0.968	0.359	0.680
Das Gupta [18]	1.89RBC – 0.33RDW – 3.28	> 0	0.707	0.628	0.335	0.667
Telmissani – MDHL [75]	$\frac{MCH \times RBC}{MCV}$	>1.75	0.214	0.994	0.208	0.604
Jayabose-RDWI [33]	$\frac{MCV \times RDW}{RBC}$	<220	0.547	0.945	0.492	0.746
Huber– Herklotz [27]	$\frac{MCH \times RDW}{10RBC} + RDW$	< 20	0.051	0.954	0.005	0.503
Sirdah [72]	$MCV - RBC - 3Hb$	<27	0.371	0.999	0.370	0.685
Kerman-I [15]	$\frac{MCH \times MCV}{RBC}$	<300	0.388	0.969	0.357	0.679
Ehsani [20]	$MCV - 10 \times RBC$	<15	0.538	0.989	0.528	0.764
Wongprachum [81]	$\frac{MCV \times RDW}{RBC} - 10Hb$	<104	0.454	0.917	0.371	0.686
Nishad [54]	$0.615MCV + 0.518MCH + 0.446RDW$	<59	0.589	0.968	0.557	0.778
Sirachainan [71]	$1.5Hb - 0.05MCV$	>14	0.167	0.679	-0.154	0.423
Bordbar [11]	$\lvert 80 - MCV \rvert \times \lvert 27 - MCH \rvert$	>44.76	0.428	0.816	0.224	0.578
Ravanbakhsh-F2 [61]	$RDW - 3RBC$	< 1.5	0.523	0.646	0.169	0.584
Ravanbakhsh-F3 [61]	$MCV \times RDW - 100RBC$	< 600	0.528	0.915	0.443	0.721
Ravanbakhsh-F4 [61]	$\frac{MCV \times Hb}{RDW \times RBC}$	< 10	0.874	0.858	0.731	0.866
Kandhro-2 [36]	$\frac{5RDW}{RBC}$	< 16.8	0.558	0.644	0.202	0.601
Merdin-1 [52]	$\frac{RDW \times RBC}{MCV}$	> 1.27	0.568	0.949	0.518	0.759
Merdin-2 [52]	$\frac{RDW \times RBC \times Hb}{MCV}$	> 14.7	0.380	0.985	0.366	0.683
Roth [64]	$\frac{1.45(MCV - 82.8)}{10.28} + \frac{0.66(MCH - 27.0)}{3.9} + 0.98$	< 0	0.584	0.967	0.551	0.776
SCS_{BTT} [16]	$0.2815MCV + 0.2015MCH - 0.2641RBC - 0.1693RDW + 0.0835Hb$	<24.99	1.000	0.720	0.720	0.860
Best			SCS_{BTT}	Sirdah	S&L	S&L

AUC, area under the curve; Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean cell volume; RBC, red blood cell; RDW, RBC distribution width; ROC, receiver operating characteristic; YI, Youden's Index.

deficiencies. RBC indices may be normal in BTT persons with coexisting megaloblastosis or co-inherited α-thalassemia. RBC counts will also be largely normal or minimally deranged in persons with sickle cell traits. On the other hand, HPLC might also be equivocal in persons with certain borderline HbA2 mutations like the CAP+1(A>C), IVS-1–110(G>A), which could further be affected by α-thalassemia, iron/B12/folate deficiencies as well as by hyperthyroidism or Zidovudine therapy. Therefore, a formula/MLA that ensures higher performance measures can radically improve the healthcare workflow to manage the available resources and efficiently utilize them.

It is revealed from the present study that the diagnostic performance of the formulae available is not comprehensive. In contrast to high-performance measures claimed by the respective authors, many formulae often show relatively lower performance measures when tested by others on different subjects. For example, [36] claimed that they obtained both maximum sensitivity and specificity (100%), which is not validated by other [30] as well as in the present study. Similar to [68], the present study revealed a higher performance measure for the Ricerca formula, but specificity was quite low. Still, the performance measure for some formulae found in the present study remained quite similar to that reported in the original study [6,14]. While one of the key focus of this study was to evaluate and compare the efficiency of SCS_{BTT}, we found that the specificity of this formula was low compared to the original research [16]; but still, it demonstrated 100% sensitivity. Moreover, the outcome of SCS_{BTT} can be evaluated globally (https://play.google.com/store/apps/details?id=com.something.susoka&hl=en&gl=US, accessed March 19, 2022), and especially countries such as: Brazil [58], Africa [67], where the hemoglobinopathies are rapidly spreading. The evaluation and comparative analysis support the application of BTT screening in a semi-automated manner and we recommended that the implementation of a robust and easily accessible application has the potential to be a tangible mass-screening tool for functional clinical laboratory diagnosis if it is further validated and improved with multi-centric data.

As revealed from the present study, S&L formula shows higher performance in differentiating BTTs from others, which is consistent with some other studies conducted in Sri Lanka [80], Taiwan [26], Indonesia [48]. Indeed, each high-frequency population in the world might carry a few common mutations that are unique to a particular region [44]. Therefore, we recommend developing and testing a region-specific

Table 3
Performance analysis of MLAs.

ML algorithms	Sens.	Spec.	YI	AUC-ROC
RF [83]	0.767	0.966	0.733	0.870
SVM-L [64]	0.762	0.960	0.722	0.860
LR [35]	0.750	0.951	0.701	0.850
KNN [47]	0.781	0.964	0.745	0.870
DTC [79]	0.734	0.939	0.674	0.840
ETC [59]	0.779	0.960	0.740	0.870
BC [25]	0.802	0.951	0.753	0.880
MLP [16]	0.807	0.968	0.775	0.890
SVM-RBF[64]	0.800	0.941	0.741	0.870
ADA [43]	0.855	0.966	0.821	0.910
LDA [34]	0.752	0.941	0.693	0.850
GBC [28]	0.875	0.957	0.832	0.920
ELM [45]	0.866	0.972	0.838	0.920
Best	GBC	ELM	ELM	GBC & ELM

ADA, adaboost classifier; AUC, area under the curve; BC, bagging classifier; DTC, decision tree classifier; ELM, extreme learning machine; ETC, extremely randomized trees classifier; GBC, gradient boosting classifier; KNN, k-nearest neighbor; LDA, linear discriminant analysis; LR, logistic regression; MLA, machine learning algorithm; MLP, multilayer perceptron; RBF, radial basis function; RF, random forest; ROC, receiver operating characteristic; Sens., sensitivity; Spec., specificity; SVM, support vector machine; YI, Youden's Index.

formula for a reliable and robust discrimination power.

In many countries, the law allows to opt for termination of pregnancy (https://en.wikipedia.org/wiki/Abortion_law, accessed March 29, 2022). Recent technology advancements include ultrasound-guided and invasive procedures to examine chorionic villus sampling (CVS) at about 11–13 weeks or amniotic fluid sampling (amniocentesis) at about 16–20 weeks to confirm. A high percentage of parents who had experience in managing hemoglobinopathies individuals revealed that they would opt for termination of pregnancy [57]. International organizations such as WHO and Thalassaemia International Federation still do not make any strategy for mandatory antenatal screening [76]. To our knowledge, this is the first study of BTT screening based on antenatal women data. It is found that a class of MLAs, as well as formulae, can ensure higher specificity as well as sensitivity. The expected highest prevalence of BTT will be among the relatives of patients. Because of the growing number of consanguineous marriages, we recommend initiating a national program to encourage comprehensive self-screening among relatives, at least using such a simple formula.

Our pre-analysis, presented in the Supplementary file, shows that significantly higher RBC count, Hb, and significantly decreased values of MCV found in the BTT group compared to IDA, which agreed with previous studies. Noticeably, the two well-performed formulae, SCS_{BTT} [16] and RF-4 [61] include Hb as additional parameter. Moreover, the

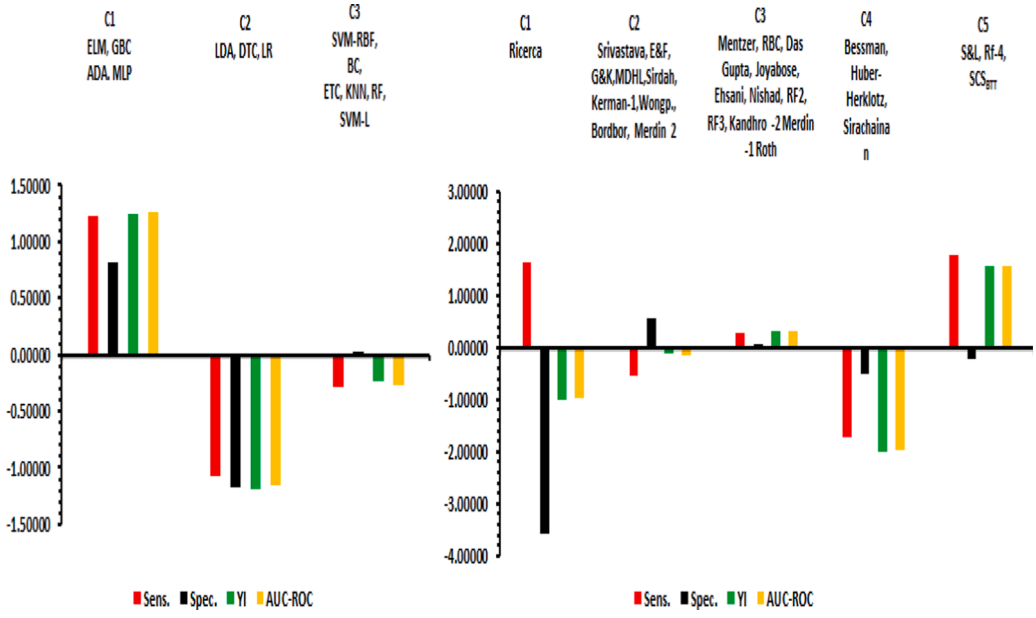

Fig. 2. K-mean cluster for formulae and MLAs.

Table 4
Final ranking of MLAs by using TOPSIS and SECA methods.

TOPSIS			SECA		
MLAs	Closeness index	Rank	MLAs	Performance of each alternatives	Rank
ELM	0.9708	1	ELM	0.9964	1
GBC	0.9678	2	GBC	0.9925	2
ADA	0.8870	3	ADA	0.9839	3
MLP	0.5940	4	MLP	0.9514	4
BC	0.4819	5	BC	0.9357	5
SVM-RBF	0.4215	6	KNN	0.9289	6
KNN	0.4118	7	SVM-RBF	0.9262	7
ETC	0.3849	8	ETC	0.9255	8
RF	0.3346	9	RF	0.9215	9
SVM (Linear)	0.2739	10	SVM (Linear)	0.9126	10
LR	0.1546	11	LR	0.8978	11
LDA	0.1185	12	LDA	0.8925	12
DTC	0	13	DTC	0.8785	13

Table 5
Final ranking of formulae by using TOPSIS and SECA methods.

TOPSIS			SECA		
MLAs	Closeness index	Rank	MLAs	Performance of each alternatives	Rank
S&L	0.9678	1	S&L	0.9432	1
SCS_{BTT}	0.9010	2	SCS_{BTT}	0.8879	2
Ravanbakhsh F4	0.8863	3	Ravanbakhsh F4	0.8846	3
Nishad	0.6554	4	Nishad	0.7604	4
Roth	0.6489	5	Roth	0.7565	5
RBC	0.6291	6	RBC	0.7430	6
Mentzer	0.6199	7	Mentzer	0.7419	7
Ehsani	0.6164	8	Ehsani	0.7395	8
Merdin-1	0.6141	9	Merdin-1	0.7342	9
Jayabose	0.5848	10	Jayabose	0.7169	10
Ravanbakhsh F3	0.5339	11	Ravanbakhsh F3	0.6844	11
Srivastava	0.4767	12	Srivastava	0.6568	12
Das Gupta	0.4697	13	Wongprachum	0.6351	13
Wongprachum	0.4490	14	Sirdah	0.6310	14
Sirdah	0.4312	15	Merdin-2	0.6285	15
Merdin-2	0.4291	16	G & K	0.6248	16
G & K	0.4245	17	Kerman-I	0.6234	17
Kerman-I	0.4220	18	Das Gupta	0.6217	18
Ricerca	0.3544	19	E & F	0.5551	19
Kandhro-2	0.3199	20	Bordbar	0.5397	20
Bordbar	0.3050	21	Kandhro-2	0.5299	21
E & F	0.3042	22	Telmissani (MDHL)	0.5201	22
Ravanbakhsh F2	0.2846	23	Ravanbakhsh F2	0.5071	23
Telmissani (MDHL)	0.2476	24	Ricerca	0.4798	24
Huber-Herklotz	0.0808	25	Huber-Herklotz	0.3826	25

formula proposed by [72], which ensures the highest specificity, also includes Hb as one of the determining parameters. The antenatal women are clinically advised to keep higher hemoglobin levels (11–16 g/DL), sometimes through additional therapy. But most of the formulae ignore the impact of Hb (Table 2). Therefore, we strongly recommend including Hb as a crucial parameter while developing a formula for BTT screening, at least for antenatal women.

Enthusiasm for applying MLAs in BTT screening mainly focuses on their potential to expedite and automate the early discrimination process. This work is also in line to evaluate how these algorithms will simulate a human clinician's decision-making processes, and when MLAs developed by training heterogeneous data can support fast and efficient mass-screening. Fig. 2; if we look at the best performing MLAs, then we have the following key observations: GBC and AdaBoost are based on *Ensemble Learning* principle, where instead of using a single predictor, multiple predictors were used and aggregated. Both MLAs are successfully implemented for multi-task learning in different fields [43,82]. However, ELM does not rely on gradient-based back-propagation principles [8,46], rather the method is based on Moore–Penrose generalized inverse principles. Therefore, the present study indicates that integrating more advanced MLAs in screening formulae and multicentric validation can yield a tangible formula. Therefore, we recommend the integration of more advanced MLAs in developing new formulae. In this regard, one of the key strengths of SCS_{BTT} is that it was developed by a hybrid algorithm (DTs and ANN) and was managed by a multidisciplinary team, and now it is open for review.

While evaluating the final recommendation, we found that a single formula or MLA fails to ensure the highest performance measure. Note that the decision-makers choice of some specific performance measure should not influence the final cut-off for formulae. A prioritization and performance measure scheme can ensure that ML algorithm or formulae can offer the potential to improve the success and efficiency of clinical research, increasing its positive impact on all stakeholders. Therefore, we recommend the use of the MCDM technique for the final recommendation from a set of criteria.

The results presented in Table 3 support the adaptability of the supervised MLAs in BTT screening in a realistic setting. However, different performance measures might likely be anomalous if hyper-parameters related to the algorithms are not set correctly. Moreover, we must also be cautious not to rely heavily on the isolated judgments made by MLAs. We intentionally did not mix the outcome of all MLAs and formulae in cluster analysis or MCDMs because: First, some of the formulae had already gone through a rigorous prospective and retrospective validation process by clinical researchers, whereas some of the MLAs, we considered in this study, were not yet validated and even implemented for BTT screening. Moreover, we used MLAs only for retrospective analysis, i.e., use historically labeled data as training and test sets. Therefore, before implementing the best-recommended MLAs (e.g., ELM), we need to conduct further trials to reduce bias and brittleness. Second, the performance of MLAs needs a specific hyper-parameter optimization scheme. Additionally, human barriers to adopting MLAs are substantial because it is difficult to set those parameters by clinicians, or sometimes there might be a scarcity of ML experts. The parameter setting might vary considerably based on the training and test sets. Therefore, standardization of hyperparameters associated with each MLAs is critical before implementing the MLAs. In this respect, we refer to [38] for the further discussion on essential barriers for direct implementation of MLAs in the clinical decision. Additionally,it is noted in EU General Data Protection Regulation (Recital 71) " *Such processing includes 'profiling' that consists '.. to obtain an explanation of the decision reached after such assessment and to challenge the decision.*" [3]. Therefore, the clear understandability of outcomes, both for patients and clinicians, is always important. How MLAs can be implemented in clinical decision-making also raises some key discussion areas: "Trustworthy AI", "Explainable AI"; a key challenge remains to ensure a stable and scalable outcome. Therefore, the intention of the present study is not to try to exceed the performance of the trained medical personnel but to show that the screening task can be performed well in a semi-automated fashion.

5. Conclusion and future research direction

Developing a screening formula is essential in diagnosing and

[3] https://eur-lex.europa.eu/eli/reg/2016/679/oj

planning to control hemoglobinopathies. This study evaluates the performance of 27 formulae and 13 MLAs using a data set of 2942 samples from antenatal females. It is revealed from the evaluation of the present data set as well as from the review of literature that the performance measures of the formulae and the MLAs might change considerably when verified on a different data set, mainly from other regions of the world. Depending on the mutations detected in different countries, the RBC-based parameters change considerably, which might affect the performance measures. Independent verification of the performance measures of the formulae and MLAs is scarce. To fully appreciate the diagnostic performance, we strongly recommend that region-specific independent verification of a formula or an MLA should be mandatory before it is used for mass screening.

This study reveals that the performance measures of the formulae S&L and SCS_{BTT} and from the MLAs, GBC and ELM are high as the ranking obtained through the SECA and TOPSIS. S&L formula has been tested on a wide variety of populations. Therefore, we recommend the use of S&L, SCS_{BTT}, GBC, and ELM for a wide range of samples. A better interpretation is possible if the best performing formulae and the MLAs could be applied together for a certain data set. However, application software is required for quick screening to validate the performance of a large data set, irrespective of the method used - formula or MLA. Finally, this study presents the first initiative of mass screening of BTT in antenatal women through this freely available software. The formula SCS_{BTT} was developed based on the data set collected form PGIMER, Chandigarh, India (Das et al. [16]). The present analysis is also conducted on data from the same institution. Therefore further evaluation is necessary on the data set collected from other independent sources, and future trials are necessary to validate the performance measures by application software if formulae and MLAs are applied jointly on a data set.

Compliance with Ethics Requirements: All procedures followed were in accordance with the ethical standards of the responsible committee (institutional) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Availability of data and materials: All relevant data are available from the authors upon reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could influenced the work reported in this paper.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijmedinf.2022.104866.

References

[1] A.S. AlAgha, H. Faris, B.H. Hammo, A.Z. Ala'M, Identifying β-thalassemia carriers using a data mining approach: The case of the Gaza Strip, Palestine, Artif. Intell. Med. 88 (2018) 70–83.

[2] S.R. Amendolia, G. Cossu, M.L. Ganadu, B. Golosio, G.L. Masala, G.M. Mura, A comparative study of k-nearest neighbour, support vector machine and multi-layer perceptron for thalassemia screening, Chemometr. Intell. Lab. Syst. 69 (1–2) (2003) 13–20.

[3] Mohammad Reza Assadi, Melikasadat Ataebi, Elmira sadat Ataebi, Aliakbar Hasani, Prioritization of renewable energy resources based on sustainable management approach using simultaneous evaluation of criteria and alternatives: A case study on Iran's electricity industry, Renew. Energy 181 (2022) 820–832.

[4] K.E. Azbari, P.S. Ashofteh, P. Golfam, V.P. Singh, Optimal wastewater allocation with the development of an SECA multi-criteria decision-making method, J. Clean. Prod. 321 (2021) 129041.

[5] M.A. Baghapour, M.R. Shooshtarian, M.R. Javaheri, S. Dehghanifard, R. Sefidkar, A.F. Nobandegani, A computer-based approach for data analyzing in hospital's health-care waste management sector by developing an index using consensus-based fuzzy multi-criteria group decision-making models, Int. J. Med. Inform. 118 (2018) 5–15.

[6] S. Bahrami, M. Rastegar, Security-based critical power distribution feeder identification: Application of fuzzy BWM-VIKOR and SECA, International Journal of Electrical Power & Energy Systems 134 (2022) 107395.

[7] G. Barnhart-Magen, V. Gotlib, R. Marilus, Y. Einav, Differential diagnostics of thalassemia minor by artificial neural networks model, Journal of clinical laboratory analysis 27 (6) (2013) 481–486.

[8] D. Barsasella, S. Gupta, S. Malwade, Y. Susanti, B. Tirmadi, A. Mutamakin, J. Jonnagaddala, S. Syed-Abdul, Predicting length of stay and mortality among hospitalized patients with type 2 diabetes mellitus and hypertension, Int. J. Med. Informatics 154 (2021) 104569.

[9] M. Behzadian, S.K. Otaghsara, M. Yazdani, J. Ignatius, A state-of the-art survey of TOPSIS applications, Expert Systems with applications 39 (17) (2012) 13051–13069.

[10] J.D. Bessman, D.I. Feinstein, Quantitative anisocytosis as a discriminant between iron deficiency and thalassemia minor. 53 (1979) 288–293.

[11] E. Bordbar, M. Taghipour, B.E. Zucconi, Reliability of different RBC indices and formulas in discriminating between beta-thalassemia minor and other microcytic hypochromic cases, Mediterranean journal of hematology and infectious diseases 7 (1) (2015).

[12] M.G. Carla, S.P. Rafael, F.G. Isabel, G.F. Cristina, S.M. Teresa, New hematologic score to discriminate beta thalassemia trait from iron deficiency anaemia in a Spanish Mediterranean region, Clin. Chim. Acta 507 (2020) 69–74.

[13] K. Chu, An introduction to sensitivity, specificity, predictive values and likelihood ratios, Emergency Medicine 11 (3) (1999) 175–181.

[14] B. Cil, H. Ayyıldız, T. Tuncer, Discrimination of β-thalassemia and iron deficiency anemia through extreme learning machine and regularized extreme learning machine based decision support system, Medical hypotheses 138 (2020) 109611.

[15] N. Cohan, M. Ramzi, Evaluation of sensitivity and specificity of Kerman index I and II in screening beta thalassemia minor, Scientific Journal of Iran Blood Transfus Organ 4 (4) (2008) 297–302.

[16] R. Das, S. Datta, A. Kaviraj, S.N. Sanyal, P. Nielsen, I. Nielsen, P. Sharma, T. Sanyal, K. Dey, S. Saha, A decision support scheme for beta thalassemia and HbE carrier screening, Journal of advanced research 24 (2020) 183–190.

[17] P.P. Das, S. Chakraborty, Application of simultaneous evaluation of criteria and alternatives (SECA) method for parametric optimization of hybrid machining processes, International Journal on Interactive Design and Manufacturing (IJIDeM) (2022) 1–13.

[18] A. Das Gupta, C. Hegde, R. Mistri, Red cell distribution width as a measure of severity of iron deficiency in iron deficiency anaemia, The Indian Journal of Medical Research 100 (1994) 177–183.

[19] F. Ecer, A consolidated MCDM framework for performance assessment of battery electric vehicles based on ranking strategies, Renew. Sustain. Energy Rev. 143 (2021) 110916.

[20] M.A. Ehsani, E. Shahgholi, M.S. Rahiminejad, F. Seighali, A. Rashidi, A new index for discrimination between iron deficiency anemia and beta-thalassemia minor: results in 284 patients, Pakistan journal of biological sciences: PJBS 12 (5) (2009) 473–475.

[21] J.M. England, P. Fraser, Differentiation of iron deficiency from thalassaemia trait by routine blood-count, The Lancet 301 (7801) (1973) 449–452.

[22] F. Esmaeilzadeh, B. Ahmadi, S. Vahedi, S. Barzegari, A. Rajabi, Major thalassemia, screening or treatment: an economic evaluation study in Iran, International journal of health policy and management. (2021) doi.10.34172/IJHPM.2021.04.

[23] R. Green, R. King, A new red cell discriminant incorporating volume dispersion for differentiating iron deficiency anemia from thalassemia minor, Blood cells 15 (3) (1989) 481–491.

[24] J.J. Hoffmann, E. Urrechaga, Role of RDW in mathematical formulas aiding the differential diagnosis of microcytic anemia, Scand. J. Clin. Lab. Invest. 80 (6) (2020) 464–469.

[25] Y.W. Hsiao, C.L. Tao, E.Y. Chuang, T.P. Lu, A risk prediction model of gene signatures in ovarian cancer through bagging of GA-XGBoost models, Journal of advanced research 30 (2021) 113–122.

[26] T.C. Huang, Y.Y. Wu, Y.G. Chen, S.W. Lai, S.C. Wu, R.H. Ye, C.S. Lu, J.H. Chen, Discrimination index of microcytic anemia in young soldiers: a single institutional analysis, PloS one 10 (2) (2015) e0114061.

[27] Huber, A., Ottiger, C., Risch, L., Regenass, S., Hergersberg, M. and Herklotz, R., 2004, September. Thalassämie-Syndrome: Klinik und Diagnose. In Swiss Medical Forum (Vol. 4, No. 38, pp. 947–952). EMH Media.

[28] M.S. Jahan, M. Mansourvar, S. Puthusserypady, U.K. Wiil, A. Peimankar, Short-term atrial fibrillation detection using electrocardiograms: A comparison of machine learning approaches, Int. J. Med. Informatics (2022) 104790.

[29] A. Jahan, G. Singh, R. Gupta, N. Sarin, S. Singh, Role of red cell indices in screening for beta thalassemia trait: an assessment of the individual indices and application of machine learning algorithm, Indian Journal of Hematology and Blood Transfusion 37 (3) (2021) 453–457.

[30] M. Jahangiri, E. Khodadi, F. Rahim, N. Saki, A. Saki Malehi, Decision-tree-based methods for differential diagnosis of β-thalassemia trait from iron deficiency anemia, Expert Systems 34 (3) (2017) e12201.

[31] M. Jahangiri, F. Rahim, A.S. Malehi, Diagnostic performance of hematological discrimination indices to discriminate between β-thalassemia trait and iron deficiency anemia and using cluster analysis: Introducing two new indices tested in Iranian population, Scientific reports 9 (1) (2019) 1–13.

[32] A. Janel, L. Roszyk, C. Rapatel, G. Mareynat, M.G. Berger, A.F. Serre-Sapin, Proposal of a score combining red blood cell indices for early differentiation of beta-thalassemia minor from iron deficiency anemia, Hematology 16 (2) (2011) 123–127.

[33] S. Jayabose, J. Giamelli, O. LevondogluTugal, C. Sandoval, F. Ozkaynak, P. Visintainer, # 262 Differentiating iron deficiency anemia from thalassemia minor by using an RDW-based index, Journal of pediatric hematology/oncology 21 (4) (1999) 314.
[34] S. Jin, D. Qin, B.S. Liang, L.C. Zhang, X.X. Wei, Y.J. Wang, B. Zhuang, T. Zhang, Z. P. Yang, Y.W. Cao, S.L. Jin, Machine learning predicts cancer-associated deep vein thrombosis using clinically available variables, Int. J. Med. Informatics 161 (2022) 104733.
[35] L.H. John, J.A. Kors, J.M. Reps, P.B. Ryan, P.R. Rijnbeek, Logistic regression models for patient-level prediction based on massive observational data: Do we need all data? Int. J. Med. Informatics 163 (2022) 104762.
[36] A. Kandhro, W. Shoombuatong, V. Prachayasittikul, P. Nuchnoi, New bioinformatics-based discrimination formulas for differentiation of thalassemia traits from iron deficiency anemia, Laboratory Medicine 48 (3) (2017) 230–237.
[37] A. Kantharaj, S. Chandrashekar, Coping with the burden of thalassemia: Aiming for a thalassemia free world, Global Journal of Transfusion Medicine 3 (1) (2018) 1.
[38] C.J. Kelly, A. Karthikesalingam, M. Suleyman, G. Corrado, D. King, Key challenges for delivering clinical impact with artificial intelligence, BMC medicine 17 (1) (2019) 1–9.
[39] M. Keshavarz-Ghorabaee, M. Amiri, E.K. Zavadskas, Z. Turskis, J. Antucheviciene, Simultaneous evaluation of criteria and alternatives (SECA) for multi-criteria decision-making, Informatica 29 (2) (2018) 265–280.
[40] G.G. Klee, V.F. Fairbanks, R.V. Pierre, M.B. O'sullivan, Routine erythrocyte measurements in diagnosis of iron-deficiency anemia and thalassemia minor, American journal of clinical pathology 66 (5) (1976) 870–877.
[41] M. Kulaphisit, J. Kampuansai, K. Leecharoenkiat, M. Wathikthinnakon, D. Kangwanpong, T. Munkongdee, S. Svasti, S. Fucharoen, D.R. Smith, P. Lithanatudom, A comprehensive ethnic-based analysis of alpha thalassaemia allelle frequency in northern Thailand, Scientific reports 7 (1) (2017) 1–9.
[42] V. Laengsri, W. Shoombuatong, W. Adirojananon, C. Nantasenamat, V. Prachayasittikul, P. Nuchnoi, ThalPred: a web-based prediction tool for discriminating thalassemia trait and iron deficiency anemia, BMC medical informatics and decision making 19 (1) (2019) 1–14.
[43] S. Li, Y. Zeng, W.C. Chapman Jr, M. Erfanzadeh, S. Nandy, M. Mutch, Q. Zhu, Adaptive Boosting (AdaBoost)-based multiwavelength spatial frequency domain imaging and characterization for ex vivo human colorectal tissue assessment, Journal of biophotonics 13 (6) (2020) e201960241.
[44] L. Loewe, W.G. Hill, The population genetics of mutations: good, bad and indifferent, Philosophical Transactions of the Royal Society B: Biological Sciences 365 (1544) (2010) 1153–1167.
[45] A. Malik, J. Iqbal, Extreme learning machine based approach for diagnosis and analysis of breast cancer, Journal of the Chinese Institute of Engineers 39 (1) (2016) 74–78.
[46] M. Mandischer, A comparison of evolution strategies and backpropagation for neural network training, Neurocomputing 42 (1–4) (2002) 87–117.
[47] G.L. Masala, B. Golosio, R. Cutzu, R. Pola, A two-layered classifier based on the radial basis function for the screening of thalassaemia, Computers in biology and medicine 43 (11) (2013) 1724–1731.
[48] A.M. Maskoen, L. Reniarti, E. Sahiratmadja, J. Sisca, S.H. Effendi, Shine & Lal index as a predictor for early detection of β-thalassemia carriers in a limited resource area in Bandung, Indonesia. BMC Medical Genetics 20 (1) (2019) 1–6.
[49] J.F. Matos, L. Dusse, K.B. Borges, R.L. de Castro, W. Coura-Vital, M.D.G. Carvalho, A new index to discriminate between iron deficiency anemia and thalassemia trait, Revista brasileira de hematologia e hemoterapia 38 (2016) 214–219.
[50] W. Mentzer, Differentiation of iron deficiency from thalassaemia trait, The lancet 301 (7808) (1973) 882.
[51] C.J.E. Metcalf, A.T. Tate, A.L. Graham, Demographically framing trade-offs between sensitivity and specificity illuminates selection on immunity, Nature Ecology & Evolution 1 (11) (2017) 1766–1772.
[52] A. Merdin, Suggestion of new formulae to be used in distinguishing beta thalasemia trait from iron deficiency anemia, Acta Med Mediter. 34 (2018) 393–395.
[53] P.K. Mishra, A. Parey, B. Saha, A. Samaddar, S. Chakraborty, A. Kaviraj, I. Nielsen, S. Saha, Production analysis of composite fish culture in drought prone areas of Purulia: The implication of financial constraint, Aquaculture 548 (2022) 737629.
[54] A.A.N. Nishad, A. Pathmeswaran, A.R. Wickramasinghe, A. Premawardhena, The Thal-index with the BTT prediction. exe to discriminate β-thalassaemia traits from other microcytic anaemias, Thalassemia Reports 2 (1) (2012) 1–2.
[55] M. Nour, H. Sindi, E. Abozinadah, Ş. Öztürk, K. Polat, A healthcare evaluation system based on automated weighted indicators with cross-indicators based learning approach in terms of energy management and cybersecurity, Int. J. Med. Informatics 144 (2020) 104300.
[56] G. Ntaios, A. Chatzinikolaou, Z. Saouli, F. Girtovitis, M. Tsapanidou, G. Kaiafa, Z. Kontoninas, A. Nikolaidou, C. Savopoulos, I. Pidonia, S. Alexiou-Daniel, Discrimination indices as screening tests for β-thalassemic trait, Annals of hematology 86 (7) (2007) 487–491.
[57] O.O. Ojewunmi, T.A. Adeyemo, O.C. Ayinde, B. Iwalokun, A. Adekile, Current perspectives of sickle cell disease in Nigeria: changing the narratives, Expert Review of Hematology 12 (8) (2019) 609–620.
[58] G.M. Olivatto, C.R.D.S. Teixeira, M.G. Sisdelli, M.L. Zanetti, R.C.D.C.P. Silveira, C. V. Gonçalves, Characterization of thalassemia major and diabetes mellitus patients at a reference center in Brazil, Hematology, Transfusion and Cell Therapy 41 (2019) 139–144.
[59] C.I. Ossai, N. Wickramasinghe, GLCM and statistical features extraction technique with Extra-Tree Classifier in Macular Oedema risk diagnosis, Biomed. Signal Process. Control 73 (2022) 103471.
[60] F. Pedregosa, G. Varoquaux, A. Gramfort, V. Michel, B. Thirion, O. Grisel, M. Blondel, P. Prettenhofer, R. Weiss, V. Dubourg, J. Vanderplas, Scikit-learn: Machine learning in Python, the Journal of machine Learning research 12 (2011) 2825–2830.
[61] M. Ravanbakhsh, S.A. Mousavi, S. Zare, Diagnostic reliability check of red cell indices in differentiating iron deficiency anemia (IDA) from beta thalassemia minor (BTT), Hormozgan Medical Journal 20 (3) (2016).
[62] B.M. Ricerca, S. Storti, G. d'Onofrio, S. Mancini, M. Vittori, S. Campisi, G. Mango, B. Bizzi, Differentiation of iron deficiency from thalassaemia trait: a new approach, Haematologica 72 (5) (1987) 409–413.
[63] R. Risoluti, S. Materazzi, F. Sorrentino, L. Maffei, P. Caprari, Thermogravimetric analysis coupled with chemometrics as a powerful predictive tool for β-thalassemia screening, Talanta 159 (2016) 425–432.
[64] I.L. Roth, B. Lachover, G. Koren, C. Levin, L. Zalman, A. Koren, Detection of β-thalassemia carriers by red cell parameters obtained from automatic counters using mathematical formulas, Mediterranean journal of hematology and infectious diseases 10 (1) (2018).
[65] M.M. Salih, B.B. Zaidan, A.A. Zaidan, M.A. Ahmed, Survey on fuzzy TOPSIS state-of-the-art between 2007 and 2017, Computers & Operations Research 104 (2019) 207–227.
[66] D. Setsirichok, T. Piroonratana, W. Wongseree, T. Usavanarong, N. Paulkhaolarn, C. Kanjanakorn, M. Sirikong, C. Limwongse, N. Chaiyaratana, Classification of complete blood count and haemoglobin typing data by a C4. 5 decision tree, a naïve Bayes classifier and a multilayer perceptron for thalassaemia screening, Biomed. Signal Process. Control 7 (2) (2012) 202–212.
[67] F.T. Shah, F. Sayani, S. Trompeter, E. Drasar, A. Piga, Challenges of blood transfusions in β-thalassemia, Blood reviews 37 (2019) 100588.
[68] C. Shen, Y.M. Jiang, H. Shi, J.H. Liu, W.J. Zhou, Q.K. Dai, H. Yang, Evaluation of indices in differentiation between iron deficiency anemia and β-thalassemia trait for Chinese children, Journal of pediatric hematology/oncology. 32 (6) (2010 1) e218–22.
[69] I. Shine, S. Lal, A strategy to detect β-thalassaemia minor, The Lancet 309 (8013) (1977) 692–694.
[70] R. Simon, Sensitivity, specificity, PPV, and NPV for predictive biomarkers, JNCI: Journal of the National Cancer Institute 107 (8) (2015).
[71] N. Sirachainan, P. Iamsirirak, P. Charoenkwan, P. Kadegasem, P. Wongwerawattanakoon, W. Sasanakul, N. Chansatitporn, A. Chuansumrit, New mathematical formula for differentiating thalassemia trait and iron deficiency anemia in thalassemia prevalent area: a study in healthy school-age children, Southeast Asian J. Trop. Med. Public Health 45 (1) (2014) 174.
[72] M. Sirdah, I. Tarazi, E. Al Najjar, R. Al Haddad, Evaluation of the diagnostic reliability of different RBC indices and formulas in the differentiation of the β-thalassaemia minor from iron deficiency in Palestinian population, International journal of laboratory Hematology 30 (4) (2008) 324–330.
[73] N. Smits, A note on Youden's Jand its cost ratio, BMC medical research methodology 10 (1) (2010) 1–4.
[74] P.C. Srivastava, J.M. Bevington, Iron deficiency and/or Thalassaemia trait, The Lancet 301 (7807) (1973) 832.
[75] O.A. Telmissani, S. Khalil, G.T. Roberts, Mean density of hemoglobin per liter of blood: a new hematologic parameter with an inherent discriminant function, Laboratory Hematology 5 (1999) 149–152.
[76] A. Thiyagarajan, S. Bhattacharya, N. Sharma, A. Srivastava, D.K. Dhar, Need for a universal thalassemia screening programme in India? A public health perspective, Journal of Family Medicine and Primary Care 8 (5) (2019) 1528.
[77] E. Urrechaga, Discriminant value of% microcytic/% hypochromic ratio in the differential diagnosis of microcytic anemia, Clinical chemistry and laboratory medicine 46 (12) (2008) 1752–1758.
[78] Urrechaga, E., Aguirre, U. and Izquierdo, S., 2013. Multivariable discriminant analysis for the differential diagnosis of microcytic anemia. Anemia, 2013.
[79] D. Wang, D.R. Willis, Y. Yih, The pneumonia severity index: assessment and comparison to popular machine learning classifiers, Int. J. Med. Informatics (2022) 104778.
[80] K.A.C. Wickramaratne, D.C. Wijewickrama, Screening for beta-thalassemia trait; applicability of red cell indices and parameters–A study in Sri Lanka, International Journal of Health Sciences 15 (1) (2021) 29.
[81] K. Wongprachum, K. Sanchaisuriya, P. Sanchaisuriya, S. Siridamrongvattana, S. Manpeun, F.P. Schlep, Proxy indicators for identifying iron deficiency among anemic vegetarians in an area prevalent for thalassemia and hemoglobinopathies, Acta haematologica 127 (4) (2012) 250–255.
[82] P. Wongyikul, N. Thongyot, P. Tantrakoolcharoen, P. Seephueng, P. Khumrin, High alert drugs screening using gradient boosting classifier, Scient. Rep. 11 (1) (2021) 1–24.
[83] S. Xu, Z. Pan, A novel ensemble of random forest for assisting diagnosis of Parkinson's disease on small handwritten dynamics dataset, Int. J. Med. Informatics 144 (2020) 104283.