Comparison of Diagnostic Performance of Classification Trees and Hematological Discrimination Functions for Differential Diagnosis between the Two Common Hematologic Disorders: An Application of Multidimensional Scaling and Cluster Analysis

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Comparison of Diagnostic Performance of Classification Trees and Hematological Discrimination Functions for Differential Diagnosis between the Two Common Hematologic Disorders: An Application of Multidimensional Scaling and Cluster Analysis

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Abstract

Background: Several hematological indices have been already proposed to discriminate between iron deficiency anemia (IDA) and β-thalassemia trait (βTT). The aim of the present study was to compare the diagnostic performance of different hematological discrimination indices with statistical methods such as decision trees to discriminate IDA from βTT.

Methods: Consisting of 1178 patients with hypochromic microcytic anemia (708 patients with βTT and 470 patients with IDA), this cross-sectional study intended to compare the diagnostic performance of 43 hematological discrimination indices and tree-based methods such as J48, CART, Evtree, Ctree, QUEST, CRUISE as well as GUIDE to discriminate IDA from βTT. Moreover, multidimensional scaling and cluster analysis were used to identify the homogeneous subgroups of discrimination methods with similar performances.

Results: All the classification tree algorithms showed acceptable accuracy measures for discrimination between IDA and βTT in comparison with other hematological discrimination indices. The results indicated that CRUISE tree algorithm had better diagnostic performance and efficiency among other discrimination methods. In turn, this tree algorithm showed the high Youden's index (88.03%), accuracy (94.57%), diagnostic odds ratio (311.63) and F-measure (95.54%) in the differential diagnosis of IDA from βTT. In addition, AUC of this algorithm indicated more precise classification with a value of 0.94 and this model was found to have excellent diagnostic accuracy. Also, CRUISE tree algorithm showed that Mean corpuscular volume can be considered as the main variable in discrimination as it extracted six homogenous subgroups of patients.

Conclusions: CRUISE tree algorithm as a powerful method in data mining techniques can be used to develop accurate differential methods along with other laboratory parameters to discriminate IDA from βTT.

Keywords: Diagnosis, classification tree algorithms, hematological discrimination indices, iron deficiency anemia (IDA), β-thalassemia trait (βTT).

1. Background

Anemia is a predominant hematologic disorder and microcytic anemia is the most common form of anemia. IDA and βTT are the two common types of microcytic anemia disorders (1, 2). The discrimination between IDA and βTT is a vital issue in hematology studies (3, 4). IDA is a prevalent disorder worldwide and βTT is in turn predominant in the Mediterranean region (10-5).

The discrimination between these two hematologic disorders is important to prevent iron overload and its complications caused by misdiagnosis and inaccurate treatment as well as to determine the prenatal causes for hemoglobin chain disorders. Although, the discrimination between these two disorders is important, the differential diagnose of IDA from βTT is a major challenge because these disorders provide similar experimental conditions (3, 11, 12).

In addition to Complete Blood Count (CBC), different tests have been already conducted to exactly differentiate between IDA and βTT; however, they are time-consuming and expensive. The definitive diagnostic methods for the IDA and βTT are respectively based on the increase in HbA2 (Hemoglobin A2), the increase in TIBC (total iron binding capacity) and also the decrease in serum iron and serum ferritin (16-13 ,11 ,4).

Due to the importance of discriminating between these types of anemia, various studies have been conducted since 1973 to propose appropriate, rapid and low-cost differential indices for discriminating between IDA and βTT (17-41).

Recently, the accessibility of powerful statistical software programs has paved the way for the application of advanced statistical models such as data mining techniques in differential diagnosis. However, few studies have already used such advanced statistical methods and data mining techniques for differential diagnosis of hematological data (40, 57-66). Therefore, this paper aims at comparing tree algorithms as powerful machine-learning methods with hematological indices in differentiation between IDA and βTT. Tree-based methods can determine homogeneous subgroups of patients needing different treatment strategies or diagnostic tests. Thus, these methods are useful for subgroup analysis (70-73).

The tree-based methods include nonparametric methods and need no assumptions about the functional form of the data. In addition, dealing with high-order interactions and nonlinear relationships, these methods are invariant to monotone transformations of predictor variables, and are robust to outliers, missing values, and also multicollinearity.In addition, one of the advantages of tree algorithms is easy to interpret due to display result as graphically and

understanding result without requiring to have statistical experience. So, these methods can also assist the clinician in decision making (74-78).

This study was intended to compare the diagnostic performance of classification tree algorithms such as Classification and Regression Tree (CART) (69), Quick, Unbiased and Efficient Statistical Tree (QUEST) (79), Classification Rule with Unbiased Interaction Selection and Estimation (CRUISE) (80), J48 (81), Generalized, Unbiased, Interaction Detection and Estimation (GUIDE) (82), Conditional Inference Trees (Ctree) (83) and Evolutionary learning of globally optimal classification and regression trees (Evtree) (84) with hematological discrimination indices to distinct between IDA and βTT by using accuracy measures such as true positive rate (TPR or sensitivity), true negative rate (TNR or specificity), false positive rate (FPR), false negative rate (FNR), accuracy, Youden's index, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (PLR), diagnostic odds ratio (DOR), F-measure and area under the curve (AUC).

Besides, multidimensional scaling was applied to extract homogeneous subgroups of hematological discriminating indices and classification tree algorithms with a similar performance according to the accuracy measures used.

2. Methods

2.1 . Sample and disease type

The present study included 1178 patients with hypochromic microcytic anemia from Boghrat clinical center in Tehran, Iran. CBC analysis of EDTA-K2 anti-coagulated blood samples was performed using Sysmex kx-21 automated hematology analyzer to measure hematological parameters such as Hb (Hemoglobin), HCT (hematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), MCHC (Mean Corpuscular Hemoglobin Concentration), RBC (Red Blood Cell Count) and RDW (Red Blood Cell Distribution Width). In addition, HbA2, TIBC, serum iron and serum ferritin were measured for all patients.

2.2. Inclusion criteria

Patients with hypochromic microcytic anemia (MCV < 80 fL ,MCH < 27 pg), Hb < 12 g.dl for women and Hb < 13 g.dl for men were included in the study. Among them, 708 patients were diagnosed as βTT with HbA2 > 3.5%, and 470 patients were diagnosed as IDA with serum ferritin < 15 ng/ml according to the World Health Organization [WHO] (68, 69).

2.3. Exclusion criteria

Patients with simultaneous presentation of the both diseases, severe anemia (Hb < 8 g.dl), anemia due to chronic disease, infectious disease, chronic inflammation, pregnancy or other hemoglobinopathies were excluded.

2.4. Statistical analysis

2.4.1. Descriptive statistics and univariate analysis

Descriptive statistics (mean, standard deviation (SD), median and interquartile range (IQR)) were evaluated for different blood parameters. Normality of data was assessed using Shapiro-wilk test. Mann–Whitney U test was also used to compare the differences between the hematological parameters of both groups (IDA and βTT). $P < 0.05$ was considered to be statistically significant.

2.4.2. Hematological discriminating indices for discriminating between IDA and βTT

Hematological indices for discrimination between IDA and βTT were computed for each patient according to their formula and cut off. These indices with their formula are shown in Table 1 (this table can be found in the supplementary file).

2.4.3. Classification tree algorithms

Classification tree algorithms such as CART (69), QUEST (79), CRUISE (80), J48 (81), GUIDE (82), Ctree (83) and Evtree (84) were used to discriminate IDA from βTT. The reduced error pruning (REP) method was used for tree pruning in the J48 tree algorithm.

2.4.4. Accuracy measures

Diagnostic performance of discrimination indices were compared with classifications tree algorithms using accuracy measures like: sensitivity, specificity, FPR, FNR, PPV, NPV, Youden's Index, accuracy, PLR, NLR, DOR, F-measure and AUC. The discrimination method with sensitivity, specificity, PPV, NPV, Youden's Index, accuracy, F-measure and AUC near to 1 provided better performance. Likewise, the discrimination method with PLR > 10, NLR < 0.1 and high DOR caused a good performance for discriminating between IDA from βTT (85, 86). Receiver operating characteristic (ROC) curve analysis was used to ompute the AUC, and compare the value of AUC of discrimination methods (87).

2.4.5. Multidimensional scaling

Multidimensional scaling method is used to create a map based on the Euclidean distance for showing similarity or dissimilarity between observations. This map can be in one dimension, two dimensions, and three dimensions or in a higher dimensions. Smaller distance among two observations indicates more similar and vice versa. The present study used a map in two dimensions for showing similarity/dissimilarity among pairs of discrimination methods through accuracy measures such as sensitivity, specificity, PPV, NPV, Youden's Index, accuracy, PLR, NLR, F-measure and AUC (89).

2.4.6. Cluster analysis

Cluster analysis is a method for extracting homogeneous subgroups of observations. Different algorithms are proposed for cluster analysis. In the present study, complete-linkage hierarchical algorithm was used to determine homogeneous subgroups of methods with a similar diagnostic performance using accuracy measures. The optimal number of methods with a similar diagnostic performance was selected using 30 appropriate measures. Finally, the optimal number was selected based on the majority role.

2.5. Software programs and checklists

Data analysis was done using software R 4.0.0. Package epiR and package pROC were used to compute accuracy measures and ROC curve analysis, respectively. Classification tree algorithms like CART, J48, Ctree and evtree were fitted using packages rpart, Rweka, party and evtree, respectively. Software for tree algorithms like QUEST, CRUISE and GUIDE was obtained from www.stat.wisc.edu/~loh/. Multidimensional scaling method was fitted using package MASS. The cluster optimal number, or homogeneous groups of diagnostic discrimination methods with a similar diagnostic performances was determined using the package of NbClust. Tree structure of classification tree algorithms was drawn using LATEX. Also, this study was conducted based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies and the Standards for Reporting Studies of Diagnostic Accuracy (STARD). These checklists can be obtained from www.equator-network.org.

3. Results

This study included 1178 patients with microcytic anemia (708 (60.10%) patients and 470 (39.90%) patients were respectively diagnosed as IDA and βTT) to compare the diagnostic

performance of hematological discrimination indices with classification tree algorithms to discriminate IDA from βTT. Table 2 indicated the descriptive statistics of hematological parameters across the type of hypochromic microcytic anemia (IDA and βTT). According to this table, all variables indicated significant difference among the groups ($P < 0.001$). CRUISE, CART and GUIDE algorithms can calculate the normalized importance (%) for each predictor variable. These algorithms indicated similar ranking of hematological parameters importance. In this study, the normalized importance of variables was reported based on the classification tree algorithm with the best diagnostic performance (CRUISE algorithm). This algorithm showed that MCV and HCT variables have the highest and lowest importance for discrimination between IDA and βTT, respectively (Table 2 can be found in the supplementary file).

Figure 1 indicated that all predictor variables except HCT and RDW can be used to split the nodes of tree. First variable splitting of tree-based methods except tree algorithms such as Evtree and Ctree were based on the MCV with similar rule splitting. GUIDE and CART algorithms showed the same tree structure.

Insert Figure 1

Table 3 displays the values of accuracy measures such as sensitivity, specificity, FPR, FNR, PPV and NPV for each discrimination method (Table 3 can be found in the supplementary file).

Table 3 indicated that none of the discrimination methods are fully specific for discrimination between IDA and βTT. this table showed that Janel index and CRUISE tree algorithm have the lowest FPR (while the highest TNR and PPV). The lowest TNR belonged to the Telmissani–MCHD index, while the lowest PPV was related to the Bessman (RDW) index. Shine and Lal index and Roth index showed perfect TPR (100%) and NPV (100%) as compared to other discrimination methods. Also, these indices showed the lowest FNR and the highest FPR. The lowest TPR (the highest FNR) was related to the Bessman (RDW) index, while the lowest NPV belonged to the Pornprasert (MCHC) index. All tree classification algorithms showed good performance for discriminating between IDA and βTT based on the accuracy measures like TPR, TNR, PPV and NPV in comparison to other hematological discrimination methods (Table 3).

The values of accuracy measures such as Youden's index, accuracy, PLR, NLR, and DOR for each discrimination method are shown in Table 4. According to this table, the highest Youden's index/accuracy belonged to the CRUISE tree algorithm, while the lowest Youden's index/accuracy was for the MCHC index. Also, the highest DOR/F-measure belonged to the CRUISE tree algorithm, whereas the Roth index and Bessman (RDW) index had the lowest DOR/F-measure. Table 4 indicated that only CRUISE has tree algorithm PLR > 10 and discrimination methods with NLR < 0.1 were all tree algorithms and indices such as Shine and Lal, Bordbar, Sehgal and Kerman I.

Insert Table 4

The value of discrimination method AUC for discrimination between IDA and βTT is shown in Table 5. The ROC analysis showed that CRUISE tree algorithm and MCHC index have respectively the highest and lowest AUC. According to the AUC, CRUISE tree algorithm indicates excellent diagnostic accuracy, whereas MCHC index could not be useful for discrimination between IDA and βTT. Table 5 indicated that AUC of all indices except indices such as Ricerca, Telmissani–MCHD, Huber–Herklotz, Zaghloul1, Zaghloul2 and Kandhrol1 were significantly more than 0.5 and AUC of discrimination indices such as RDW and MCHC were significantly less than 0.5 ($P < 0.001$).

Insert Table 5

The comparison between AUC values of classification tree algorithms and hematological discrimination index with the best diagnostic performance among hematological indices (Ehsani index) indicated that there is a statistically significant difference between AUC values of classification tree algorithms and Ehsani index ($P < 0.05$). In this regard, classification tree algorithms had significantly higher AUC than the mentioned hematological discrimination index. Also, CRUISE tree algorithm had significantly higher AUC than other classification tree algorithms, but there was no significant difference between AUC values of Ctree and CART algorithms ($P > 0.05$).

Overall, the results showed that CRUISE tree algorithm has a better performance for discrimination between IDA and βTT in comparison to all indices and other classification tree methods. This tree algorithm extracted six homogenous subgroups of patients (Figure 1). According to the tree structure of CRUISE tree algorithm, it can be concluded that patients with MCV > 67.65 or 67.65 <MCV ≤ 71.25 & Hb ≤ 11.15 or MCV ≤ 67.65 & Hb ≤ 8.85 & MCHC ≤ 30.32 were classified as βTT. Also, patients with 67.65 < MCV ≤ 71.25 & Hb

> 11.15 or MCV ≤ 67.65 & Hb > 8.85 or MCV ≤ 67.65 & MCHC > 30.32 were classified as IDA.

In addition, multidimensional scaling method extracted three subgroups of methods. The diagram of this analysis is shown in Figure 2. One group included hematological discrimination indices such as Pornprasert, RDW, Kandhrol1, Huber−Herklotz, Sirachainan, Hameed, Zaghloul1 and Zaghloul2. While the other group included Shine and Lal, Roth, Ricerca and Telmissani–MCHD. The third group in turn included classification tree algorithms and some of hematological discrimination indices.

Insert Figure 2

Cluster analysis like multidimensional scaling method extracted three homogenous groups of discrimination methods. The diagram of this analysis is shown in Figure 3.

Insert Figure 3

4. Discussion

The two common types of microcytic anemia disorders are IDA and βTT which have similar clinical and experimental conditions (3, 11, 12). The discrimination between these two disorders is clinically important needing time-consuming and expensive tests like HbA2, serum iron, serum ferritin and TIBC (16-13 ,11 ,4). Several hematological indices are proposed for rapid and low-cost discrimination between IDA and βTT which are not fully sensitive and specific for differential diagnose (17-41).

The present study used classification tree algorithms to discriminate between IDA and βTT. These are efficient and low-cost detection methods to extract homogeneous subgroups of patients (70-73). Thus, the diagnostic performance of hematological indices was compared with tree-based methods to differentiate IDA and βTT using various accuracy measures.

Additionally, multidimensional scaling was used to extract homogeneous subgroups of methods with a similar performance based on the mentioned criteria.

The findings showed that none of the mentioned discrimination methods are fully sensitive and specific in discrimination between IDA and βTT. Also, tree-based methods exhibited high performance for differential diagnosis in comparison with the other hematological indices. CRUISE tree algorithm indicated better performance than other discrimination methods based on the amount of accuracy measures such as Youden's index, accuracy, PLR, NLR, DOR, F-measure and AUC. These criteria included both sensitivity and specificity and indicated the

diagnostic performance of discrimination method more accurately than other criteria. So, this algorithm can help physicians make better clinical decision.

Although, sensitivity of hematological discrimination indices such as Ricerca, Telmissani – MCHD, Bordbar, Roth and Shine and Lal (S&L) was higher than CRUISE tree algorithm, these hematological indices had a high false positive rate as compared to the CRUISE tree algorithm. Also, with respect to the other measurements, these indices had poor performance to discriminate between IDA and βTT.

Consistent with the findings of the present study, other studies demonstrated that Ehsani index had good performance in discrimination between these two disorders in comparison with other hematological indices (56 ,43). Meta-analysis studies indicated that Bessman (RDW) index had a low AUC in comparison to other hematological indices (90, 91).

Overall, the findings showed that CRUISE tree algorithm had better performance in discrimination between IDA and βTT as compared to all hematological discrimination indices and other classification tree methods. Moreover, comparison between the AUC of CRUISE tree method and Ehsani index (this index had best diagnostic performance in comparison to the other hematological indices) showed that there is a statistically significant difference between AUC of these two discrimination methods ($P < 0.001$); CRUISE had significantly higher AUC than this discrimination index. Indeed, all accuracy measures indicated that CRUISE tree algorithm had best diagnostic performance among the discrimination methods used.

Tree-based methods were fitted using hematological parameters as predictor variables. Based on the results obtained from CRUISE tree method, MCV was the main hematological predictor parameter in differentiation between different types of hypochromic microcytic anemia. In this regard, it was found that the patient with βTT had lower values of MCV. In a previous study which used different decision trees for discrimination between IDA and βTT, the first split of all algorithms was based on the MCV indicating that MCV was an important predictor variable in discrimination of IDA and βTT (61).

Several studies proposed various tree-based methods for differential diagnostic between microcytic anemia (57, 58, 61, 64-66). For instance, Bellinger et al. used classification algorithms like J48 decision tree, support vector machines (SVM), k-nearest neighbours (K-NN), multilayer perceptron (MLP) and naïve Bayes (NB) to discriminate between patients with IDA and βTT or both (64). In another study, Setsirichok evaluated the classification of blood characteristics by a C4.5 decision tree, a NB classifier and a MLP for classifying eighteen classes of thalassemia abnormality (57). Likewise, Jahangiri et al. used classification tree algorithms for constructing differential scheme and investigating the performance of several

tree algorithms for the differential diagnosis of IDA from βTT. In agreement with the present study, they indicated that CRUISE tree algorithm had the highest AUC and MCV was an important predictor variable in the discrimination of observations into IDA and βTT and first split of all algorithms was based on of MCV (61). Moreover, Chakraborty et al. utilized Ada-boost algorithm to generate multiple decision trees by using C4.5 decision tree for classification of erythrocytes or anemia detection. Their proposed approach showed accuracy, specificity and sensitivity of 97.81%, 99.7% and 97.33% respectively in detecting abnormal erythrocytes (65). Comparing the diagnostic performance of several algorithms such as J48, K-NN, artificial neural networks and NB for identifying β-thalassemia carriers, AlAgha concluded that naïve Bayes had the superior performance to distinct between normal and β-thalassemia carriers (66). Using advanced methods such as tree-based methods for discriminating between IDA and βTT addition to the differential indices can be a good idea for discriminating between these two hematologic disorders. Though each index only includes one or specific blood parameters, machine learning methods can consider the effects of all blood parameters simultaneously for data prediction and exploratory modeling. Besides, using decision trees for discrimination between IDA and βTT can avoid expensive, time-consuming, and complicated laboratory procedures leading to non-satisfactory hematological indices in discriminating between these two hematologic disorders.

The application of methods like multidimensional scaling and cluster analysis are deemed to be useful to determine different classification methods with a similar diagnostic functions. In previous hematological studies, such indices were compared subjectively based on the accuracy measures. Therefore, the application of multidimensional scaling method and cluster analysis are proposed to determine the hematological discrimination indices with similar performance for future hematological studies.

5. Conclusions

Given its diagnostic performance, CRUISE tree algorithm is considered as an appropriate method for differential diagnosis of patients in comparison to other methods. Moreover, tree-based methods are useful along with other parameters for discriminating between IDA and βTT. In conclusion, considering the advantages of tree algorithms, they can help physicians make better clinical decision.

Declarations

Ethics approval and consent to participate

Present study was approved by the ethical code IR.NIMAD.REC.1398.389 from the National Institute for Medical Research Development, Tehran, Iran. A written informed consent was obtained before the enrollment. All methods were performed in accordance with the relevant guidelines and the institution regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Table Legends

Table 4. Youden's index, accuracy, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostoc odds ratio (DOR) of each hematological index and classification tree algorithm for differentiation between iron deficiency anemia (IDA) and β-thalassemia trait (βTT) with their 95% confidence interval.

Discriminant method	Youden's Index (%)	Accuracy (%)	PLR	NLR	DOR
CART/GUIDE	81.58 (76.26−86.05)	91.51 (89.77−93.04)	7.39 (5.83−9.37)	0.07 (0.05−0.09)	114.12 (75.09−173.43)
J48	85.12 (80.27−89.07)	93.38 (91.81−94.73)	8.41 (6.54−10.81)	0.04 (0.03−0.06)	219.56 (133.69−360.55)
QUEST	79.96 (74.43−84.65)	90.49 (88.67−92.11)	7.37 (5.79−9.36)	0.09 (0.07−0.11)	86.09 (58.24−127.27)
CRUISE	88.03 (83.52−91.59)	94.57 (93.12−95.79)	11.09 (8.28−14.86)	0.04 (0.02−0.05)	311.63 (184.41−526.62)
Ctree	81.23 (75.85−85.75)	91.26 (89.49−92.81)	7.47 (5.88−9.49)	0.07 (0.05−0.09)	105.13 (69.81−158.29)
Evtree	83.49 (78.44−87.66)	92.61 (90.97−94.04)	7.65 (6.02−9.72)	0.05 (0.03−0.07)	169.18 (106.14−269.64)
England and Fraser (E&F)	48.82 (41.84−55.22)	71.65 (68.98−74.21)	5.097 (3.96−6.56)	0.44 (0.40−0.49)	11.44 (8.33−15.70)
RBC	54.89 (47.68−55.22)	79.03 (76.59−81.32)	2.80 (2.44−3.22)	0.21 (0.18−0.26)	13.28 (9.98−17.68)
Mentzer	71.25 (64.95−76.81)	86.33 (84.24−88.24)	4.99 (4.10−6.06)	0.13 (0.11−0.16)	37.66 (26.96−52.60)
Srivastava	58.83 (51.84−65.18)	78.44 (75.98−80.76)	4.74 (3.83−5.86)	0.30 (0.26−0.34)	15.70 (11.62−21.20)
Shine and Lal (S&L)	15.32 (11.66−18.90)	66.21 (63.43−68.91)	1.18 (1.14−1.23)	0	Inf
Bessman (RDW)	-15.83 (-21.04 − -10.61)	34.38 (31.67−37.17)	0.20 (0.13−0.30)	1.20 (1.14−1.26)	0.17 (0.11−0.26)
Ricerca	3.70 (0.04−7.52)	60.95 (58.09−63.75)	1.04 (1.01−1.07)	0.46 (0.27−0.78)	2.28 (1.31−3.97)
Green and King (G&K)	62.21 (55.29−68.47)	81.15 (78.80−83.35)	4.25 (3.52−5.13)	0.23 (0.20−0.27)	18.42 (13.68−24.81)
Das Gupta	32.87 (26.06−39.44)	71.48 (68.80−74.04)	1.56 (1.44−1.69)	0.21 (0.16−0.27)	7.52 (5.46−10.36)
Jayabose (RDWI)	57.28 (50.30−63.70)	80.64 (78.27−82.86)	2.83 (2.47−3.25)	0.17 (0.13−0.21)	17.01 (12.57−23.02)
Telmissani – MCHD	2.78 (-0.68−6.40)	60.61 (57.76−63.41)	1.03 (1−1.06)	0.52 (0.30−0.90)	1.99 (1.11−3.57)
Telmissani – MDHL	40.70 (33.65−47.24)	66.81 (64.04−69.50)	4.36 (3.38−5.61)	0.54 (0.49−0.58)	8.11 (5.93−11.10)
Huber – Herklotz	6.02 (-15.26−11.98)	46.10 (43.22−48.99)	1.47 (1.11−1.95)	0.93 (0.89−0.98)	1.58 (1.14−2.20)
Kerman I	60.66 (54.29−66.44)	83.28 (81.02−85.36)	2.77 (2.44−3.14)	0.08 (0.06−0.11)	35.83 (24.36−52.68)
Kerman II	72.96 (66.78−78.37)	86.93 (84.87−88.80)	5.63 (4.56−6.96)	0.13 (0.11−0.16)	42.01 (29.89−59.03)
Sirdah	70.86 (64.73−76.21)	84.38 (82.18−86.41)	8.57 (6.45−11.38)	0.22 (0.19−0.25)	39.28 (27.37−56.37)
Ehsani	73.38 (67.24−78.75)	87.18 (85.14−89.04)	5.67 (4.58−6.99)	0.13 (0.10−0.16)	43.85 (31.12−61.79)

Continue on next page

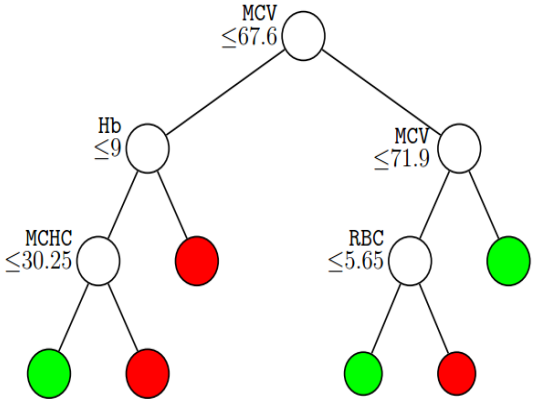
Table 4 (Continued)

Discriminant method	Youden's Index (%)	Accuracy (%)	PLR	NLR	DOR
Bordbar	55.05 (49.02−60.56)	81.58 (79.25−83.75)	2.29 (2.06−2.55)	0.04 (0.03−0.07)	54.87 (32.80−91.82)
Matos and Carvalho	57.27 (50.15−63.77)	77.93 (75.45−80.27)	4.20 (3.45−5.13)	0.30 (0.27−0.35)	13.89 (10.38−18.58)
Janel (11T)	67.62 (61.41−73.08)	82.26 (79.95−84.40)	8.95 (6.63−12.07)	0.26 (0.23−0.30)	34.29 (23.75−49.50)
CRUISE Index	41.87 (34.09−49.23)	72.24 (69.59−74.78)	2.18 (1.92−2.48)	0.35 (0.30−0.41)	6.21 (4.80− 8.05)
Index26	71.07 (64.87−76.50)	84.81 (82.63−86.81)	7.55 (5.81−9.81)	0.20 (0.17−0.24)	37.23 (26.29−52.72)
Hisham	51.70 (44.32−58.58)	77.25 (74.75−79.62)	2.66 (2.32−3.06)	0.25 (0.21−0.29)	10.66 (8.09−14.05)
Hameed	11.68 (5.73−17.35)	48.81 (45.92−51.71)	2.25 (1.64−3.08)	0.87 (0.83−0.91)	2.58 (1.80−3.69)
Ravanbakhsh-F1	54.11 (46.87−60.80)	78.69 (76.24−80.99)	2.74 (2.39−3.15)	0.22 (0.18−0.26)	12.74 (9.59−16.94)
Ravanbakhsh-F2	32.29 (24.46−39.83)	68.68 (65.94−71.32)	1.69 (1.53−1.88)	0.39 (0.34−0.47)	4.26 (3.30−5.50)
Ravanbakhsh-F3	50.98 (43.74−57.73)	77.76 (75.27−80.10)	2.43 (2.14−2.75)	0.21 (0.17−0.25)	11.74 (8.81−15.65)
Ravanbakhsh-F4	46.34 (39.79−52.48)	77.50 (75.01−79.86)	1.96 (1.78−2.16)	0.10 (0.08−0.14)	18.87 (12.99−27.42)
Zaghloul1	4.35 (-3.32−11.86)	47.96 (45.08−50.86)	1.16 (0.97−1.39)	0.94 (0.87−1.01)	1.23 (0.95−1.59)
Zaghloul2	3.27 (-4.43−10.85)	47.54 (44.65−50.44)	1.12 (0.93−1.34)	0.96 (0.89−1.03)	1.17 (0.91−1.51)
Kandhrol1	-4.91 (-1.31− 3.40)	48.89 (46.01−51.79)	0.92 (0.83−1.01)	1.12 (0.98−1.28)	0.82 (0.65−1.04)
Kandhrol2	30.29 (22.67−37.66)	68.59 (65.85−71.24)	1.58 (1.44−1.74)	0.37 (0.31−0.45)	4.28 (3.29−5.57)
Alparslan	38.71 (31.29−45.79)	72.67 (70.02−75.19)	1.82 (1.65−2.02)	0.27 (0.22−0.33)	6.77 (5.13−8.94)
Merdin1	58.60 (51.48−65.09)	79.20 (76.77−81.49)	3.89 (3.25−4.69)	0.27 (0.23−0.31)	14.68 (11.01−19.59)
Merdin2	46.40 (39.10−53.16)	70.97 (68.28−73.55)	3.95 (3.18−4.90)	44.93 (40.56−49.76)	8.79 (6.57−11.75)
Roth	14.89 (11.28−18.44)	66.04 (63.26−68.75)	1.18 (1.13−1.22)	0	Inf
Sargolzaie	29.79 (22.21−36.99)	61.63 (58.78−64.42)	2.57 (2.10−3.15)	0.63 (0.58−0.69)	4.07 (3.09−5.35)
Keikhaei	59.29 (52.21−65.76)	80.31 (77.92−82.54)	3.51 (2.97−4.14)	0.22 (0.19−0.26)	15.69 (11.75−20.95)
Nishad	63.96 (57.17−70.09)	82.94 (80.66−85.04)	3.81 (3.22−4.51)	0.17 (0.14−0.21)	22.16 (16.32−30.09)
Wongprachum	55.33 (48.04−62.05)	78.35 (75.89−80.67)	3.15 (2.69−3.69)	0.26 (0.22−0.30)	12.36 (9.34−16.34)
Sehgal	64.70 (58.66−70.10)	85.23 (83.07−87.21)	3.027 (2.65−3.46)	0.05 (0.03−0.07)	60.80 (38.73−95.44)
Pornprasert (MCHC)	-32.50 (-40 − -24.65)	31.32 (28.68−34.06)	0.40 (0.34−0.47)	1.71 (1.54−1.90)	0.23 (0.18−0.30)
Sirachainan	9.45 (2.23−16.46)	49.58 (46.68−52.47)	1.48 (1.19−1.83)	0.88 (0.83−0.94)	1.68 (1.27−2.21)

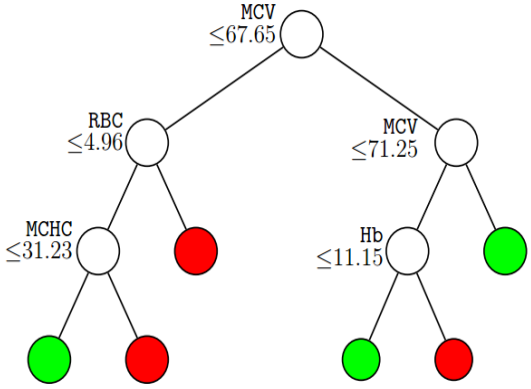
Table 5. F-measure and AUC of each hematological index and classification tree algorithm for differentiation between iron deficiency anemia (IDA) and β-thalassemia trait (βTT) with their 95% confidence interval.

Discriminant method	F-measure (%)	AUC	Standard Error	95% CI	p–value
CART/GUIDE	93.04	0.908	0.009	0.891 – 0.925	< 0.001
J48	94.61	0.926	0.008	0.909 – 0.942	< 0.001
QUEST	92.12	0.889	0.009	0.882 – 0.918	< 0.001
CRUISE	95.54	0.940	0.007	0.926 – 0.955	< 0.001
Ctree	92.80	0.906	0.009	0.889 – 0.924	< 0.001
Evtree	93.99	0.918	0.009	0.901 – 0.934	< 0.001
England and Fraser (E&F)	72.03	0.744	0.012	0.721 – 0.767	< 0.001
RBC	83.02	0.774	0.013	0.749 – 0.799	< 0.001
Mentzer	88.69	0.856	0.011	0.836 – 0.877	< 0.001
Srivastava	80.61	0.794	0.012	0.771 – 0.817	< 0.001
Shine and Lal (S&L)	78.06	0.577	0.008	0.560 – 0.593	< 0.001
Bessman (RDW)	6.76	0.421	0.009	0.401 – 0.440	< 0.001
Ricerca	74.89	0.519	0.007	0.505 – 0.532	0.281
Green and King (G&K)	83.84	0.811	0.012	0.788 – 0.834	< 0.001
Das Gupta	79.39	0.664	0.013	0.639 – 0.689	< 0.001
Jayabose (RDWI)	84.62	0.786	0.012	0.762 – 0.811	< 0.001
Telmissani – MCHD	74.76	0.514	0.006	0.502 – 0.526	0.419
Telmissani – MDHL	65.67	0.704	0.012	0.679 – 0.727	< 0.001
Huber – Herklotz	29.52	0.530	0.011	0.509 – 0.551	0.080
Kerman I	87.22	0.803	0.012	0.780 – 0.826	< 0.001
Kerman II	89.08	0.865	0.010	0.845 – 0.885	< 0.001
Sirdah	86.06	0.854	0.010	0.835 – 0.874	< 0.001
Ehsani	89.31	0.867	0.010	0.847 – 0.887	< 0.001
Keikhaei	83.49	0.797	0.012	0.773 – 0.820	< 0.001
Nishad	85.93	0.819	0.012	0.797 – 0.843	< 0.001
Wongprachum	81.83	0.777	0.013	0.752 – 0.801	< 0.001
Sehgal	88.72	0.824	0.011	0.801 – 0.846	< 0.001
Pornprasert (MCHC)	27.57	0.337	0.014	0.305 – 0.370	< 0.001
Sirachainan	41.07	0.547	0.013	0.523 – 0.572	0.006
Bordbar	86.43	0.775	0.012	0.752 – 0.798	< 0.001
Matos and Carvalho	80.36	0.786	0.012	0.763 – 0.809	< 0.001
Janel (11T)	83.76	0.838	0.010	0.818 – 0.858	< 0.001
CRUISE	77.02	0.709	0.014	0.683 – 0.736	< 0.001
Index26	86.63	0.855	0.010	0.835 – 0.875	< 0.001
Hisham	81.39	0.759	0.013	0.733 – 0.784	< 0.001
Hameed	33.07	0.558	0.010	0.538 – 0.578	0.001
Ravanbakhsh-F1	82.77	0.771	0.013	0.746 – 0.795	< 0.001
Ravanbakhsh-F2	75.12	0.661	0.014	0.634 – 0.689	< 0.001
Ravanbakhsh-F3	82.42	0.755	0.013	0.729 – 0.779	< 0.001
Ravanbakhsh-F4	83.49	0.732	0.012	0.708 – 0.756	< 0.001
Zaghloul1	42.01	0.522	0.014	0.495 – 0.548	0.207
Zaghloul2	41.81	0.516	0.014	0.489 – 0.543	0.341
Kandhrol1	56.06	0.475	0.015	0.447 – 0.504	0.153
Kandhrol2	75.88	0.671	0.014	0.644 – 0.697	< 0.001
Alparslan	79.04	0.694	0.013	0.668 – 0.719	< 0.001
Merdin1	81.99	0.793	0.012	0.769 – 0.817	< 0.001
Merdin2	72.01	0.732	0.012	0.708 – 0.756	< 0.001
Roth	77.97	0.574	0.008	0.558 – 0.591	< 0.001
Sargolzaie	60.42	0.649	0.013	0.623 – 0.674	< 0.001

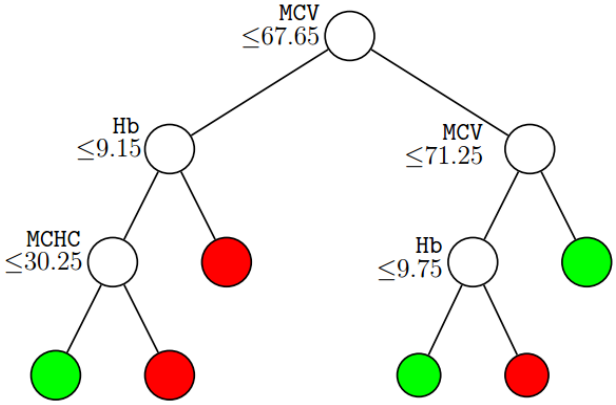
Figure Legends



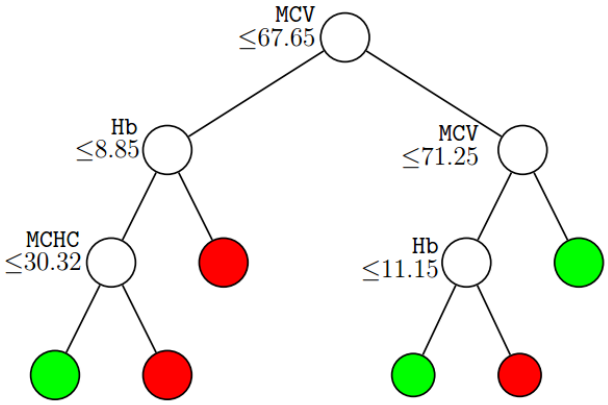
J48 algorithm



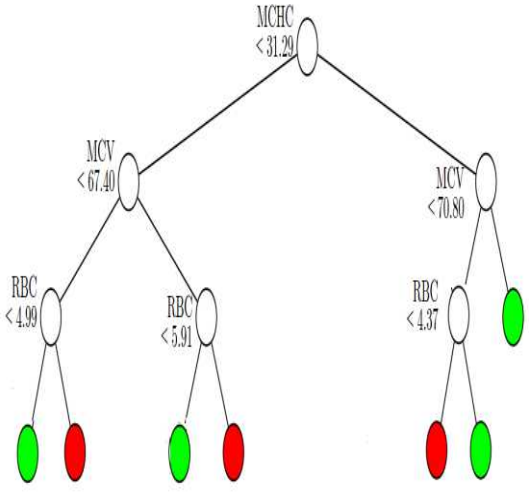
CART and GUIDE algorithm



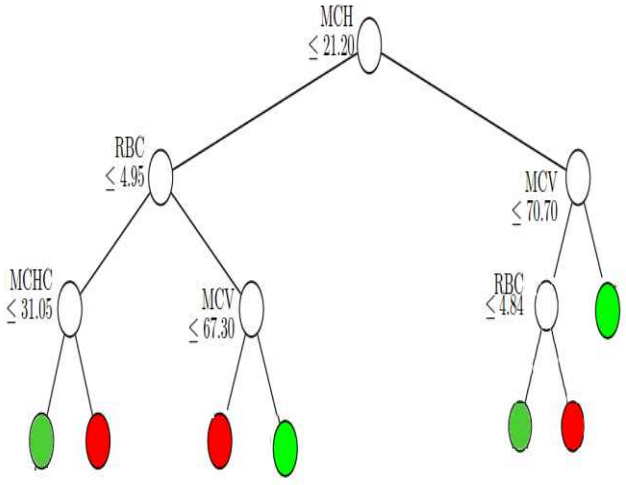
QUEST algorithm



CRUISE algorithm



Evtree algorithm



Ctree algorithm

Figure 1. Tree structure of classification tree algorithms (red: βeta thalassemia trait and green: iron deficiency anemia)

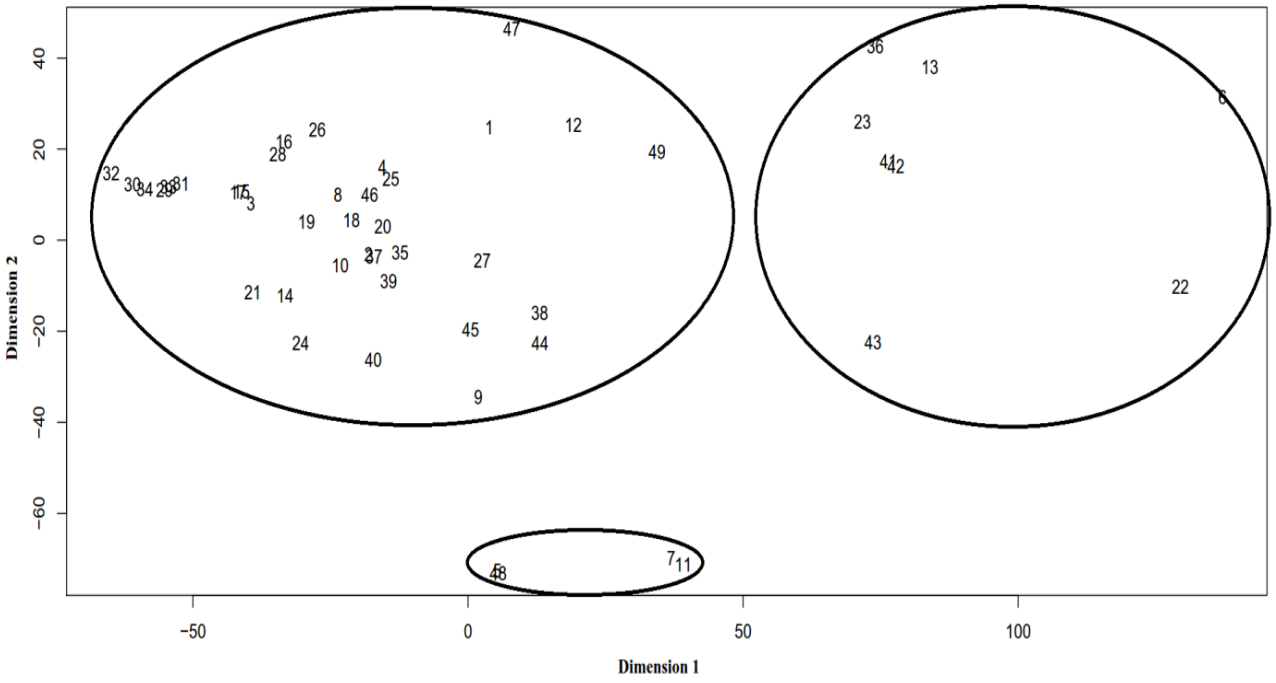


Figure 2. Diagram of multidimensional scaling for extracting homogeneous groups of hematological indices and classification tree algorithms with a similar diagnostic performance (1:England and Fraser, 2:RBC, 3:Mentzer, 4:Srivastava, 5:Shine and Lal, 6:Bessman (RDW), 7:Ricerca, 8:Green and King, 9:Das Gupta, 10:Jayabose (RDWI), 11:Telmissani–MCHD, 12:Telmissani–MDHL, 13:Huber–Herklotz, 14:Kerman I, 15:Kerman II, 16:Sirdah, 17:Ehsani, 18:Keikhaei, 19:Nishad, 20:Wongprachum, 21:Sehgal, 22:Pornprasert, 23:Sirachainan, 24:Bordbar, 25:Matos and Carvalho, 26:Janel (11T), 27:CRUISE Index, 28:Index26, 29:CART/Guide, 30:J48, 31:QUEST, 32:CRUISE, 33:Ctree, 34:Evtree, 35:Hisham, 36:Hameed, 37:Ravanbakhsh-F1, 38:Ravanbakhsh-F2, 39:Ravanbakhsh-F3, 40:Ravanbakhsh-F4, 41:Zaghloul1, 42:Zaghloul2, 43:Kandhrol1, 44:Kandhrol2, 45:Alparslan, 46:Merdin1, 47:Merdin2, 48:Roth, 49: Sargolzaie).

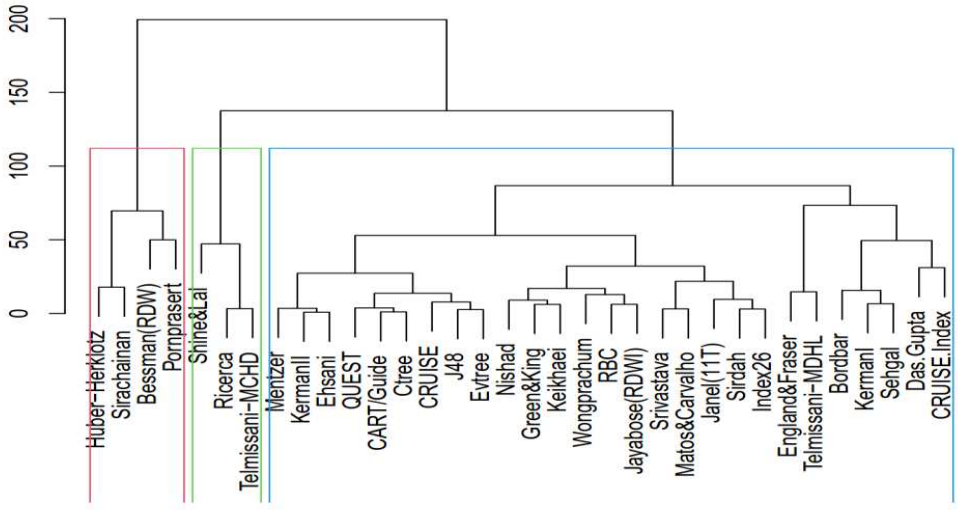


Figure 3. Dendrogram of cluster analysis for extracting homogeneous groups of hematological discrimination indices and classification tree algorithms with the same diagnostic performance (each rectangles includes discrimination methods with a similar diagnostic performance).

Figures

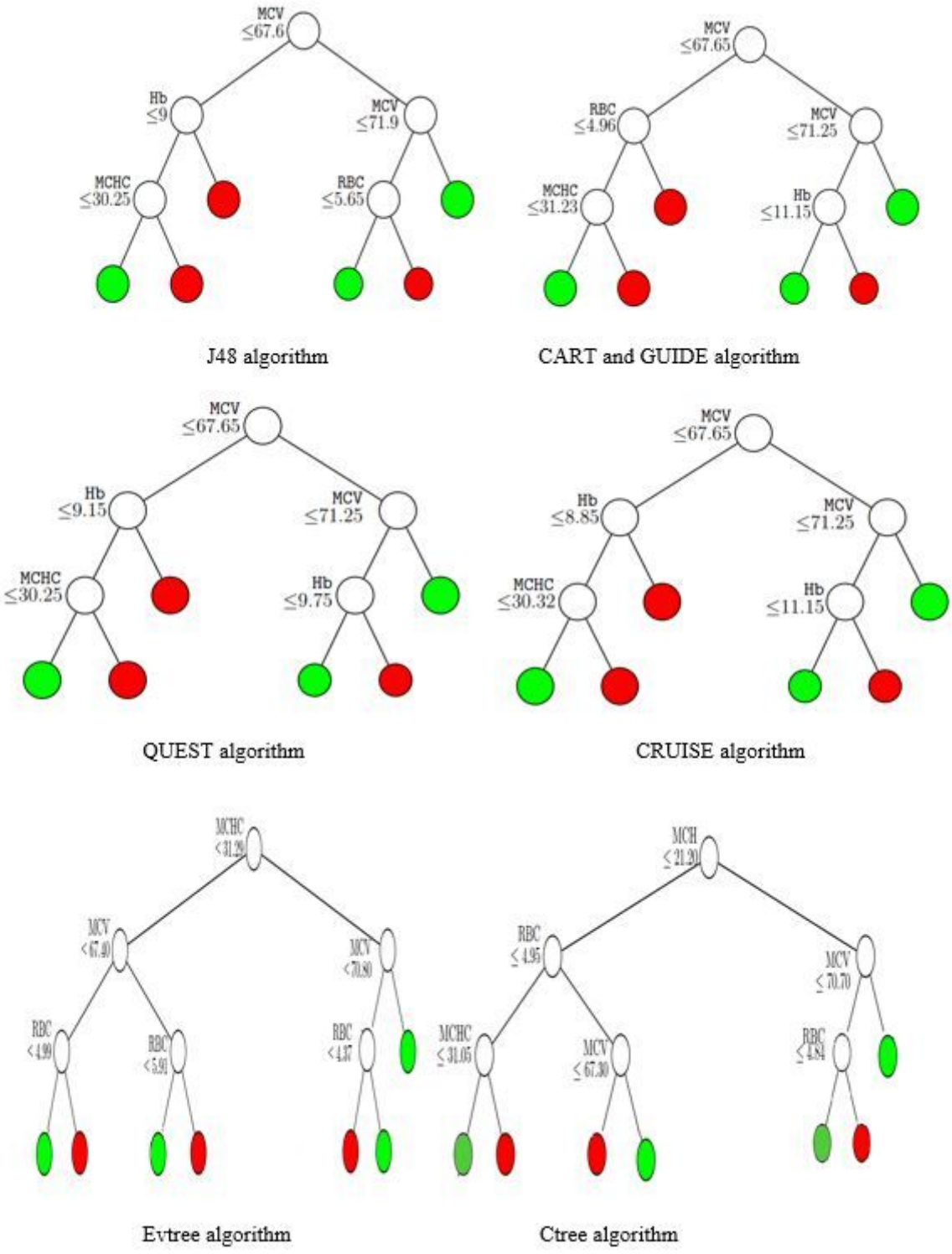


Figure 1

Tree structure of classification tree algorithms (red: βeta thalassemia trait and green: iron deficiency anemia)

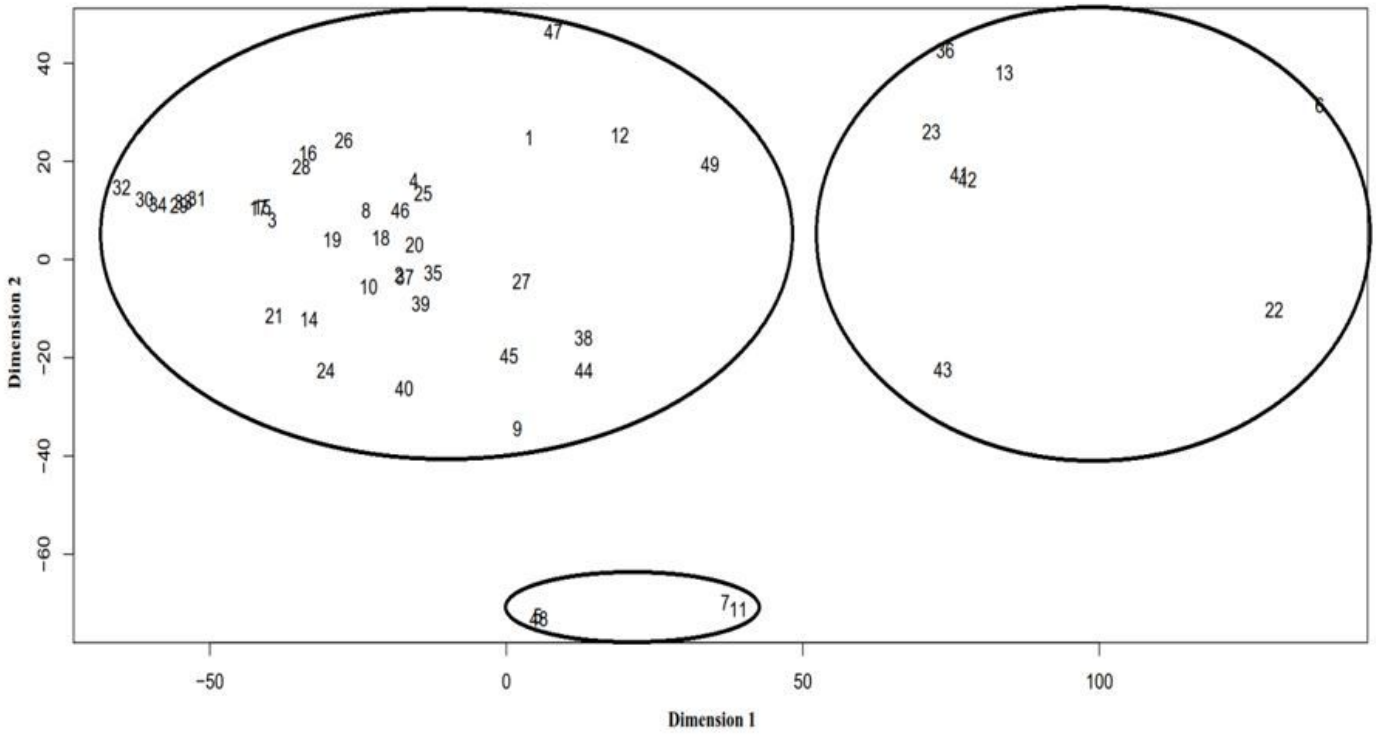


Figure 2

Diagram of multidimensional scaling for extracting homogeneous groups of hematological indices and classification tree algorithms with a similar diagnostic performance (1:England and Fraser, 2:RBC, 3:Mentzer, 4:Srivastava, 5:Shine and Lal, 6:Bessman (RDW), 7:Ricerca, 8:Green and King, 9:Das Gupta, 10:Jayabose (RDWI), 11:Telmissani–MCHD, 12:Telmissani–MDHL, 13:Huber–Herklotz, 14:Kerman I, 15:Kerman II, 16:Sirdah, 17:Ehsani, 18:Keikhaei, 19:Nishad, 20:Wongprachum, 21:Sehgal, 22:Pornprasert, 23:Sirachainan, 24:Bordbar, 25:Matos and Carvalho, 26:Janel (11T), 27:CRUISE Index, 28:Index26, 29:CART/Guide, 30:J48, 31:QUEST, 32:CRUISE, 33:Ctree, 34:Evtree, 35:Hisham, 36:Hameed, 37:Ravanbakhsh-F1, 38:Ravanbakhsh-F2, 39:Ravanbakhsh-F3, 40:Ravanbakhsh-F4, 41:Zaghloul1, 42:Zaghloul2, 43:Kandhrol1, 44:Kandhrol2, 45:Alparslan, 46:Merdin1, 47:Merdin2, 48:Roth, 49: Sargolzaie).

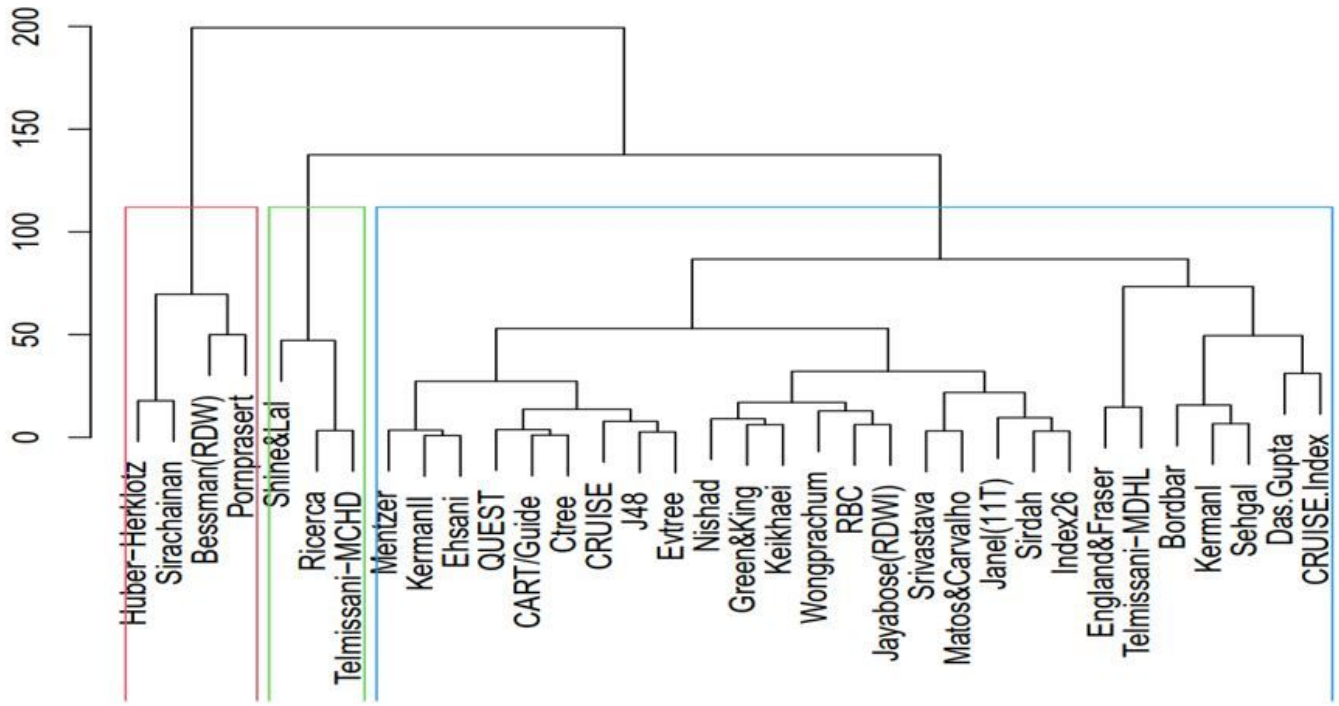


Figure 3

Dendrogram of cluster analysis for extracting homogeneous groups of hematological discrimination indices and classification tree algorithms with the same diagnostic performance (each rectangles includes discrimination methods with a similar diagnostic performance).

Supplementary Files

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