Differential microcyte anemia diagnosis using hierarchical soft computing

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Abstract

Anemia is the most common hematological disorder. It's difficult to discriminate either thalassemia or Iron deficiency anemia, due to the two subtype of microcytic anemia, which has the feature similarly with mean cell volume less than 80 fL (fluid ounces). The CBC is objective for physician to discriminate anemia between iron deficiency anemia with thalassemia. The disorder will be more serious when physicians cannot identify to therapy adequately.

Applied soft computing to solve problem of classification such as Fuzzy C-means, Competitive learning gain for more attentions, and Adaptive neural-fuzzy inference system, that parallels the human mind to process information under imprecision and uncertain circumstance. Soft computing is fitting to discriminate based on CBC result of the microcytic diagnosis under imprecision and uncertain. After ANFIS pruning rule, this paper find: (1) There is 98% accuracy inferred in 50 confirmed cases by ANFIS reasoning, which is more accurate than traditional experience. (2) Under sensitivity and specificity, sensitivity is 90%, and specificity is 95.8% higher than others discriminant function when employ ANFIS with 13 rules, and inference value is 13.6.

Keywords: **Hierarchical soft computing, microcyte anemia, ANFIS pruning rule, reasoning.**

1.Introduction

The microcytic anemia is the most common hematological disorder encountered in Taiwan, over one billion peoples are anemic in the world. Anemia, the red blood cell mass reduce to which caused the hemoglobin diminish the capability of oxygen carrying, which could be lead to death if anemic disorder developed to acute anemia rapidly. The symptoms in patients with anemia are those of underlying disease present fatigue, syncope, dyspnea, angina pectoris and transient cerebral, etc.[3] In approaching the evaluation of anemia, physicians depend on complete blood cell counts (CBC) to find anemia that hemoglobin (HGB) and hematocrit (HCT) levels below the normal reference range, the iron deficiency anemia (IDA) and thalassemia (THA) characterized microcytic anemia with mean cell volume (MCV) of CBC less than 80 fL. In general, physicians discriminate either IDA or THA that is difficultly upon review the result of CBC, due to the two subtypes of microcytic anemia, that the feature of IDA similar to the THA, for discriminate effectively, the patient must accept to do others further examination. The CBC of patients for differential diagnosis of anemia considered that is ambiguous, approximate and possible, for example a patient under MCV equal to 78, HGB equal to 11 and HCT equal to 36 that it could be considered as IDA. Since 1973, Mantzer proposed discriminant function (DF) which MCV/RBC less than 13 is THA more likely [22], the uncertain and imprecision explained in sensitivity and specificity, subsequently, more DFs proposed e.g. England et al studied the discrimination between thalassemia and iron deficiency anemia using DF based on MCV, HGB concentration and RBC [7], who proposed formulation MCV-RBC-(5xHGB)-k; k denotes constant adjusted by different population. Most of the DFs formulated with RBC and other items of CBC to calculate outcome of which used for microcytic anemia classification. These DFs can only identify either IDA or THA more accurately, because the result that have many false positive or false negative [2,19].

Soft computing aims at problem of classification, which different from traditional hard computing with mass and complex mathematical formulation. The microcytic anemia classified in statistical DFs depends on the automatic analyzer to support the more parameters but it's insufficient for physicians to classify correctly. The expert knowledge implied in CBC dataset, which mined in hierarchical soft computing (HSC) for anemic diagnosis. HSC is suitable for machine learning incorporate with the cognition of expert. This paper employs the artificial soft computing in hierarchical top-down to extract rules, which is systematic underlying the linguistic items imprecision and uncertain. Traditionally, in order to confirm the anemia strictly that need not only to review CBC result but also consider serum-iron and examine the HbA2 (Hemoglobin electrophoresis) additional if the clinical physician could not discriminate them explicitly [3,19]. Through the context, this paper adapts the CBC criteria referred to World Health Organization (WHO) published, and source of dataset referred to automatic analyzer CEL-DYN 1700 and Sysmex TX2000i.

This paper organized 5 sections, section 2 overview the soft computing methods e.g. FCM, Competitive Learning, ANFIS and anemic differential diagnosis. Section 3 we propose a hierarchical framework combine soft computing method base on the characteristic of anemia attempt to find rules of microcytic anemic diagnosis. Section 4, verify the hierarchical framework with collected dataset of CBC and be comparisons between the result of hierarchical framework and DF proposed statistically. Finally, from above result be a conclusion to end of this paper.

2.Preliminary

Soft computing differs from conventional (hard) computing in that, unlike hard computing, it is tolerant of imprecision, uncertainty, partial truth, and approximation. In effect, the role model for soft computing is the human mind. The guiding principle of soft computing is: Exploit the tolerance for imprecision, uncertainty, partial truth, and approximation to achieve tractability, robustness and low solution cost. The basic ideas underlying soft computing in its current incarnation have links to many earlier influences, among them Zadeh's 1965 paper on fuzzy sets; the 1973 paper on the analysis of complex systems and decision processes; and the 1979 report (1981 paper) on possibility theory and soft data analysis. The inclusion of neural computing and genetic computing in soft computing came at a later point [10,11,12,13].

2.1 FCM

The FCM algorithm proposed by Bezdek, it aims to find fuzzy partitioning of a given training set, by minimizing a fuzzy generalization of the least squares functional. To determine appropriate algorithm of cluster depend on the specified question and knowledge for the supervision of cluster [1], the algorithm of cluster not only used to analysis data classification or organization, and it's useful on data compression and modeling [7].

FCM partition a vector data $x_i, i = 1,..., n$ into cluster c, and find the center of each group as the cost function of dissimilarity measure minimum. The difference of HCM and FCM that is degree of partition data point into some cluster, it determined by membership function in [0, 1]. Eq. (1) is the membership function represented by u.

$$\sum u_{ij} = 1, \forall_j = 1,...n \tag{1}$$

The degree of membership function of sum dataset depends on the condition of normalization.

$$J(U, c_1,..., c_c) = \sum_{i=1}^{c} J_i = \sum_{i=1}^{c}\sum_{j=1}^{n} u_{ij}^m d_{ij}^2 \tag{2}$$

Hence $u_{ij} \in [0,1]$, c_i is the cluster center of i th; $d_{ij} = \|c\_x_j\|$ is the Euclidean distance from i node to j. $m \in [1, \infty)$ is the exponent of weight. After Bezdek some literatures proposed membership function. Eq. (3) is the membership of FCM.

$$u_{ij} = \frac{1}{\sum_{k=1}^{c}\left(\frac{d_{ij}}{d_{kj}}\right)^{2/(m-1)}} \tag{3}$$

2.2 Competitive learning networks

The competitive learning network is a popular scheme to achieve this type of unsupervised data clustering or classification. When no external supervisor or critic's instruction available, only input vectors can be used for learning. Such an approach is unsupervised learning, or system evolves to extract features or regularities in presented patterns, without being told what outputs or classes associated with the input patterns are desired [7].

The dimensions equal to number of inputs and the number of outputs is number of clusters partitioned

Input vector $x = [x_1, x_2, x_3]^T$ and weight vector $w_J = [w_{1j}, w_{2j}, w_{3j}]^T$ unit of output j often assumed normalized the length of neuron. The activation strengthens of unit j a_j is input vector calculated by the inner product of the input and weight vectors.

$$a_j = \sum x_i w_{ij} = x^T w_j = w_j^T x. \tag{4}$$

It selected to be further process when the output units have the highest activation strengthens. Suppose the output unit k has the maximum activation values, the weight will update according to the competitive or the so-called "winner take all" learning rule.

$$w_k(t+1) = \frac{w_k + \eta(x(t) - w_k(t))}{\|w_k(t) + \eta(x(t) - w_k(t))\|}. \tag{5}$$

Weights updated Eq. (5) when the output unit k is winner, and others weight value unchanged where η is learning rate refers to Eq. (8). To be dissimilarity measure use Euclidean distance referred to Eq. (6) that is the popular architecture. The activation of output unit j:

$$a_j = \left(\sum (x_i - w_{ij})^2\right)^{0.5} = \|x - w_j\|. \tag{6}$$

The output units update activation value with minimum weight update by:

$$w_k(t+1) = w_k(t) + \eta(x(t) - w_k(t)). \tag{7}$$

The step size or learning rate η varies by time (t), which often calculated by formula where α is adjustable parameter for stability:

$$\begin{cases} \eta(t) = \eta_0 e^{-\alpha t}, \text{with} : \alpha > 0, \text{or} \\ \eta(t) = \eta_0 t^{-\alpha}, \text{with} : \alpha <= 1, \text{or} \\ \eta(t) = \eta_0(1 - \alpha t), \text{ with} : 0 < \alpha < (\max\{t\})^{-1}. \end{cases} \tag{8}$$

2.3 ANFIS

Adaptive Neural-Fuzzy Inference System called for short ANFIS stands for adaptive network-based fuzzy inference system functionally equivalent to fuzzy inference system [7]. It maps input and output of the expert knowledge and use the hybrid learning or back propagations method to generate the parameters set of the fuzzy membership function of if-then rule.

Layer1: Every node of this layer is an adaptive node with activation. The x, y is the linguistic label (such as "small" or "large") of input unit with respect to the node. $\text{Output}_{1,i}$ is the membership function A1,A2 of fuzzy set and it specifies degree to given input x or y. For example Eq. (11) is membership of bell Where {a, b, c} is the parameter set. As the values of these parameters change, the bell-shaped function varies accordingly. Parameters in this layer are referred to as premise parameters.

$\text{Output}_{1,i} = \mu Ai(x)$ for i=1,2, or (9)

$$\text{Output}_{1,i} = \mu B_{i-2}(y) \quad \text{for } i=3,4, \tag{10}$$

Membership function:

$$\mu_A(x) = \frac{1}{1+\left|\frac{x-c_i}{a_i}\right|^{2b}} \tag{11}$$

Layer2: Every node of this layer is a fixed node. It sums all of input signs; each one of outputs represents the firing strength of a rule. The operator employed maximum (or), minimum (and), product or others T-norm.

$$O_{2,i} = t(\mu_{Ai}(x), \mu_{Bi}(y)) \qquad = \mu_{Ai}(x) \times \mu_{Bi}(y) = \omega_i \tag{12}$$

Layer3: Every node of this layer is fixed node. The ith node calculates the ratio of the ith rule's firing strength to sum of all rules' firing strengthens. The output of this layer are called normalized firing strengthens. The ith of this layer output:

$$O_{3,i} = \varpi_i = \frac{\omega_i}{\omega_1 + \omega_2} \tag{13}$$

Layer4: Every node is the adaptive node with a node function. The ith node output of this layer:

$$O_{4,i} = \varpi_i f_i = \varpi_i (p_i x + q_i y + r_i) \tag{14}$$

Eq.13 where ϖ_i is a normalized firing strengthen from layer 3 and $\{p_i q_i r_i\}$ is the parameters which referred be the consequence parameters.

Layer5: Every node of this layer is fixed node, the output function sum all of incoming signals. The output of net is consequent liner combination if the antecedent parameter is fixed.

$$O_{5,i} = \sum_i \varpi_i f_i = \frac{\sum_i \omega_i f_i}{\sum_i \omega_i} \tag{15}$$

Output of node will forward to $4th$ layer. The consequences parameters with least square estimator forward learning and validate error back propagate to ith layer. Premise parameters with gradient descent method back propagation learning. The advantage is that can optimize the premise parameters and consequence parameters of this procedure.

2.4 Diagnosis of Microcytic anemia

The original meaning of the word "anemia" is misunderstood from without blood, and definition of anemia is the mass of red blood cell reduce, response to the hemoglobin concentration in blood reduce. It's not a diagnosis but a sign of a pathological process or disease [19]. The cause of anemia arises from acute or chronic disease, which must rolled out the hemoglobin concentration change abnormal, it may produce higher hemoglobin concentration and red blood cell count when the hematocrit reduces.

Anemic diagnosis based on HGB and HCT values below the normal reference range which is followed by anemic classification based on (1) MCV (2) Automated analyzer (3) Symptoms of patient list [14]. The clinical physicians to differential diagnosis of anemia, first if the hemoglobin in blood the weight per dL lower than 12 g/dL. Figure 1 is the procedures of the anemic diagnosis.

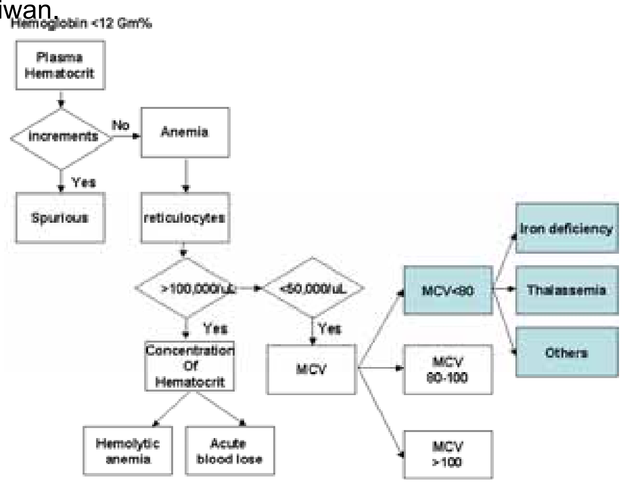

Figure 1. Anemia diagnosis procedures

The mean cell hematocrit (MCH) is the ratio of hemoglobin and red blood cell count (RBC million/uL), and mean cell hematocrit concentration (MCHC) is the ratio of hemoglobin and hematocrit. These items referred to the degree of anemia.

The HCT is the index, which specifies the degree of anemia. In general, HCT determined by multiplying the RBC times the MCV. Red blood cell distribution width (RDW) is a marker of aberrant red cell morphologies and RDW not enough be a major index of different type shape. RBC morphology provides unique diagnostic information in only 4 to 6% anemia cases, and there are 25% be used for assist to diagnose [14]. In general RDW is the coefficient of variation of the MCV and HCT [13]. It is helpful to differentiate between IDA and THA when exclude the RDW distribute curve tail of cell width size too small.

3. Hierarchical soft computing

The soft computing is an innovative approach that parallels the remarkable ability of the human mind to reason and learn from an environment of uncertainty and imprecision. [12] HSC method, namely, the complex problem of classification solved in some soft computing methods top-down hierarchical, each one procedure adopt specific method which is in Artificial Neural Network, Fuzzy set theory, Neuro-Fuzzy Modeling, and other method of derivative-Free optimization like GA and simulated annealing, etc. Undoubtedly, the HSC is suitable for microcytic anemia diagnosis from the point of view that is multi-procedure, supervised or unsupervised. The HSC for anemic cluster, which separated into some stages to extract rule exist in the CBC for constructing an inference system. The HSC aims at the anemic diagnostic procedures, which the result of every stage propagated to the input of next stage for inference system.

3.1 Procedures of HSC

The pathological anemia diagnosis can only discriminate on blood cell size. The HSC procedures extend the procedures of anemic diagnosis detailed. In order to mine the knowledge exist in CBC dataset that a soft computing method adopt by a procedure of HSC, which depend on expert knowledge and characteristic of dataset. The architecture of HSC shown in Figure 2, which comprise four procedures following:

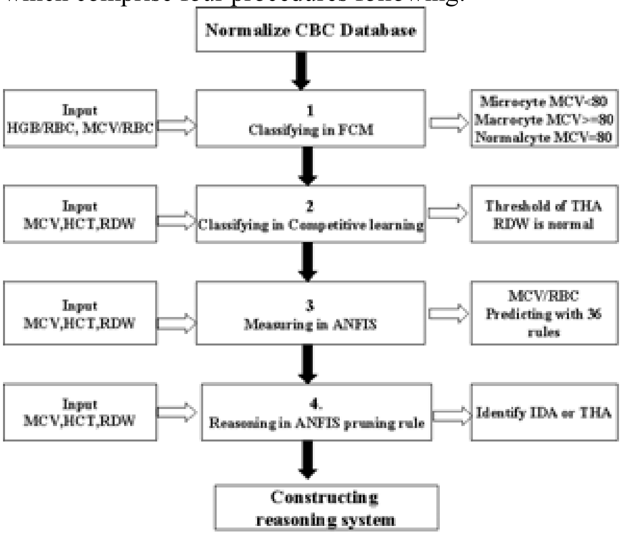

Figure 2. Architecture of HSC

4.1 Verifying progress

The sub section highlight the progress on implemented steps of each stage, that describe individual method to process cluster, and settle the parameters given under formal range of input.

4.1.1. Verifying in FCM. This stage employ FCM to classify for anemia on blood cell size referred to flowchart of anemic diagnosis referred to Figure 1. Initially, we adopt pre-computed values MCV/RBC and HGB/RBC to classify. The progress below:

1. Assigning the input variables MCV/RBC and HGB/RBC pre-compute depend on the discipline mentioned in section 2.4.
2. Cluster numbers specified to correspond with the three subtypes of anemia on blood size.
3. Eliminating patterns with MCV larger than 80 fL.

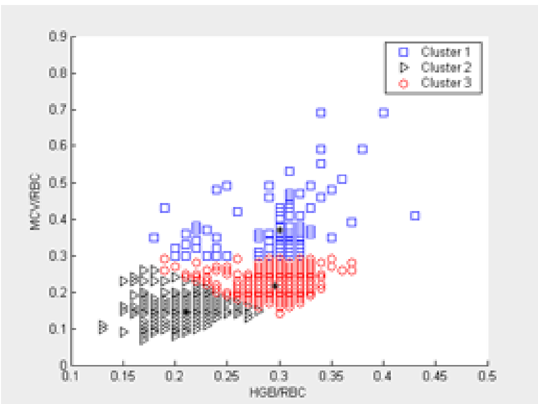

Figure 3. Cluster #2 is microcyte, which classified in FCM

At result shown in Figure 3, the No. 2 cluster is microcyte that MCV less than 80 fL, there are 5 patterns MCV over 80 fL among 430 records, the 425 patterns be propagated to next stage after exclude 5 patterns.

Inspecting the progress of FCM, there are 26 times, it iterated to decrease object function values from 4.13 to 1.86 to minimum for correcting the center of cluster. There is 99% accuracy after FCM to classify the microcytic anemia.

4.1.2. Verifying in competitive learning. The anemic CBC patterns imply the condition exist in dataset which MCV/RBC is known Mantzer for discriminate THA and IDA. End of this section, we done the experiments to compare the effect of competitive learning with others method, the competitive learning is better than other methods of the soft computing, which is adequate to learn the experience or knowledge of expert. The steps of this stage:

1. To specify the range of input variable of competitive learning. HCT from 25 to 50, MCV from 50 to 79 and RDW from 13 to 32 from picked patterns.
2. To specify three neurons of output corresponding with three anemic disorder of microcytic anemia, and three neurons of input which corresponding with three parameters.
3. To specify the kohonen learning-rate to 0.01, we try to test learning rate from 0.005 to 0.05 to find that has the least patterns misclassified.
4. The training does not converged till 100 epochs completed.

The result of competitive learning, there are three clusters classified manifestly, which the input RDW and pre-computed MCV/RBC smaller than others clusters identified. The maximum of MCV/RBC be the threshold after screened and compared that help for discriminate IDA and THA.

4.1.3 Verifying in initial ANFIS. This stage employs ANFIS for reasoning the MCV/RBC, the constraints of ANFIS proposed that (1). Have a single output and using weighted average defuzzification, all of membership function must be the same type and either liner or constant. (2). Be first or zeroth order Sugeno-type system (3). Different rule can not share the same output namely numbers of membership functions must equal to the number of rules [7]. This stage follows the constraints for organizing ANFIS to practice the prediction of MCV/RBC be output. The linguistic variables referred to the knowledge of expert for reasoning so as to finer to distinguish either THA or IDA. The linguistic terms listed in Table 1. There are total 425 patterns be input of this stage , for training adaptive neural network that use hybrid learing, which consume time cost for training with the less error validation. Thus 225 patterns picked randomly that to be training dataset, the others is test dataset. The steps following:

1. To feed matrices in dataset, which has four columns, the fourth column represent supervisor of training dataset.
2. To assign the membership functions number of MCV, HCT and RDW is 3, 4 and 3 respectively.
3. To assign type of membership function is triangle, and the learning method is hybrid learning.
4. To assign the 500 epochs to training, in general, the ANFIS provide validation via checking data set to avoid over fitting. Therefore, for less error validation that needs to increase the training epochs proportional when membership function increased.
5. To verify inference system with test dataset, whether inference value of MCV/RBC meet

the expectative result after the inference system trained complete.

Table 1. Linguistic terms representation

Input	Linguistic value
MCV	Very LOW · LOWER · LOW Slightly
HCT	Very LOW · LOWER · LOW Slightly · Not LOW
RDW	NORMAL · WIDE · WIDER

This initial ANFIS is used to train adequate fuzzy linguistic variable of inference system, and to predict MCV/RBC in the minimum error validation. Therefore in order to has minimum error validation of training, the shape Gaussian, triangular and trapezoidal specified by experimentation respectively. The topology of the ANFIS with 13 rules shown in Figure 4.

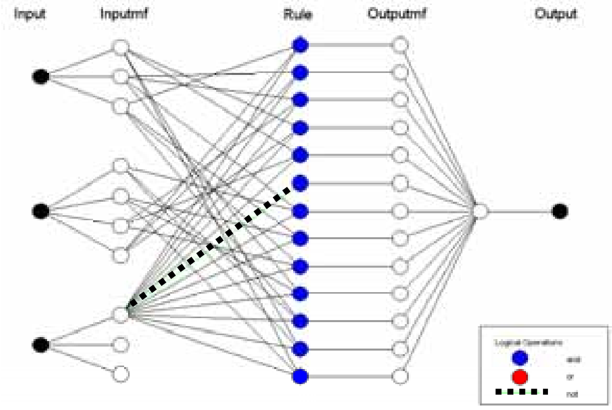

Figure 4. Architecture of ANFIS

4.1.4 Verifying in aggregated ANFIS. After trained completely, the ANFIS verified with 200 patterns. We could not discriminate the THA and IDA, depend on only a unity constant of MCV/RBC before combine the conditions proposed previous stage, it's necessary to aggregate the finding of first and second stage, in accordance with RDW value of CBCs is normal, and MCV/RBC below 14 likely THA to prune rules which listed in Table 2.

Table 2. Pruned redundant of ANFIS.

No.	MCV	HCT	RDW
1	V	V	N
2	V	L	N
3	V	S	N
4	V	N	N
5	L	V	N
6	L	L	N
7	L	S	N
8	L	N	N
9	S	V	N
10	S	L	N
11	S	S	N
12	S	N	N
13	N/A	N/A	NN

***Note V,L,S,N,NN refer to Table 1. Rule #13 ignore the MCV and HCR , and consider only RDW.**

The progress below:

1. To prune the rule fitting that meet following discipline.
2. To feed the training dataset again.
3. To assign the training epochs to 300 because there are fewer rules.

We concern the single value whether it discriminate accurate than experience of physicians effectively, hence picked 50 patterns compared with diagnosis documented on chart, there are 5 patterns after inferred different from documented on chart. The five patterns, one is ICD-9=285.9 which marked implicitly and unknown, three patterns documented ICD-9=282.4 which MCV/RBC greater than 14 calculated from CBC, but the diagnosis of physician support ANFIS result less than 14, there are two patterns ICD-9=280 documented on chart which MCV/RBC less than 14, but the diagnosis of physician support the ANFIS result greater than 14. The accurate rate is 98% of ANFIS for the explicit diagnosis of physician.

4.2 Comparison

To classify the microcytic anemia explicitly, it is necessary to select an optimal classifier from some methods of cluster that belongs to soft computing and statistical method. These methods, e.g. FCM, Competitive learning, Self-Organization-Map (SOM), K-means and Hierarchical cluster, that compared with specified condition. We specify one of the three clusters, which classified that the RDW is normal and MCV/RBC less than 14 to verify with THA condition correspond to positive result and verify with IDA condition inversely. The competitive learning and SOM classify effectively, there are 417 (98.2%) patterns differentiated among 425 patterns of microcytic anemia, FCM differentiate 412 (97%) patterns among 425 patterns next, K-means differentiated 388 (91%) patterns among 425 patterns next and the hierarchical cluster is the worst that can not cluster any one, the result listed in Table3.

Table 3. Accuracy comparison between DFs with pruned ANFIS.

Method	Type	Cluster number	correct	Accuracy
Competitive learning	Unsupervised	3	417	98.2%
K-means	Partitioning	3	388	91%
Fuzzy C-means	Unsupervised	3	412	97%
Self Organize Map (SOM)	Unsupervised	3	417	98.2%
Hierarchical	Cluster tree	1	N/A	N/A

Using DF to discriminate IDA and THA by sensitivity and specificity, the sensitivity has a trade-off relationship with specificity and there is no parameter having high values in both sensitivity and specificity for discriminate between IDA with THA [2]. However, the Mantzer combined RDW-cv satisfied patient is positive for THA, the sensitivity and specificity are 90.1% and 95.8% respectively. The range of inference value assumed that beginning from Mantzer DF to finding of previous, which divided to 10 intervals for finding the highest specificity. The result listed in Table 4.

Table 4. Comparison with DF.

DF name	Formulation	THA	SEN%	SPE%
Mentzer	MCV/RBC	<13.5	92.6%	77.4%
Srivastava	MCH/RBC	<4	69.0%	94.0%
England	MCV-5*HGB-RBC	<15	95.0%	68.9%
Bruno	0.096*MCV+0.415*RDW-0.139*RBC	<13	93.0%	52.7%
Shine-L	MCV (squared)*MCH/1000	<153	91.5%	36.4%
Our proposed	**MCV/RBC (+) RDW (cv)**	**<13.6**	**90.1%**	**95.8%**

*Note: (+) represent aggregation, DF utilize specificity and sensitivity.

5. Conclusions

More papers applied artificial intelligent to medicine study [15,16,21], we focus on the architecture, which is hierarchical, top-down and rule-based to classify microcyte in soft computing method, step by step to find knowledge exist in anemic CBCs dataset. It's adequate, for avoiding the attribute of CBCs like HGB, which is larger to affect cluster non-microcyte patterns misclassified. The FCM classify microcyte with liner discriminant perfectly, that there are only 16 patterns misclassified among 441 patterns, which has accuracy 97%. We choose the optimal method via specific condition in order to obtain feature of THA and IDA respectively. The objective of this stage, that (1) The threshold of THA, (2) Be the supervisor of ANFIS, (3) Combining RDW-cv with MCV/RBC for reasoning. We loose some precision to prune some rules to raise performance, inference system will higher after prune 23 rules that belongs to linguistic variable RDW not normal. The sensitivity is 90% and specificity is 95.8% compare with DF when the inference threshold corrected from 14 down to 13.6. The sensitivity represent the microcyte anemia found easily, and specificity represent for THA discriminated from IDA is explicitly. Our proposed better than other DFs with both higher sensitivity and specificity applied in clinic practice, and reduced the cost for anemic exam of HbA2 and serum-iron additionally. This paper proposed the hierarchical soft computing to extract feature assist physician to diagnosis, which is more institutive to help physician diagnose in time.

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