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Decision-making model for early diagnosis of congestive heart failure using rough set and decision tree approaches

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ABSTRACT

The accurate diagnosis of heart failure in emergency room patients is quite important, but can also be quite difficult due to our insufficient understanding of the characteristics of heart failure. The purpose of this study is to design a decision-making model that provides critical factors and knowledge associated with congestive heart failure (CHF) using an approach that makes use of rough sets (RSs) and decision trees. Among 72 laboratory findings, it was determined that two subsets (RBC, EOS, Protein, O2SAT, Pro BNP) in an RS-based model, and one subset (Gender, MCHC, Direct bilirubin, and Pro BNP) in a logistic regression (LR)-based model were indispensable factors for differentiating CHF patients from those with dyspnea, and the risk factor Pro BNP was particularly so. To demonstrate the usefulness of the proposed model, we compared the discriminatory power of decision-making models that utilize RS- and LR-based decision models by conducting 10-fold cross-validation. The experimental results showed that the RS-based decision-making model (accuracy: 97.5%, sensitivity: 97.2%, specificity: 97.7%, positive predictive value: 97.2%, negative predictive value: 97.7%, and area under ROC curve: 97.5%) consistently outperformed the LR-based decision-making model (accuracy: 88.7%, sensitivity: 90.1%, specificity: 87.5%, positive predictive value: 85.3%, negative predictive value: 91.7%, and area under ROC curve: 88.8%). In addition, a pairwise comparison of the ROC curves of the two models showed a statistically significant difference ($p < 0.01$; 95% CI: 2.63–14.6).

1. Introduction

The syndrome of heart failure is most commonly defined as a state in which cardiac abnormalities cause cardiac dysfunction such that the heart is unable to meet the circulatory demands of the body, or does so with elevated filling pressures [1]. Given that there is no definitive diagnostic test for heart failure, clinical diagnosis is largely based on a careful history and physical examination that are supported by ancillary tests such as chest radiography, electrocardiogram, and echocardiography. Despite advances related to the complex pathophysiology of heart failure, both its diagnosis and the assessment of therapeutic approaches remain difficult. A timely and accurate diagnosis by a physician is important in order to avoid unnecessary diagnostic procedures and to identify appropriate therapeutic measures and clinical management strategies. However, the search for meaningful sets among critical factors that can affect the early diagnosis of heart failure is difficult, due to the numerous clinical features of routinely available tests, echocardiography, etc.

Data-mining techniques can be applied to overcome effectively these limitations by using large data sets with many predictive factors in order to identify not just linear relationships, but non-linear relationships as well. In particular, the rough set theory (RST) [2] can be used as a tool to discover data dependencies [3–5] and to reduce the number of attributes contained within a data set, using the data alone, and no additional information. In RST, this attribute reduction removes superfluous features and makes it possible to

Abbreviations: SG, specific gravity; OB, occult blood; WBC, white blood cell; RBC, red blood cell; Ep. Cell, epithelial cell; HGB (Hb), hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; PLT, platelet count; NEUT, neutrophil; LYMP, lymphocyte; MONO, monocyte; EOS, eosinophil; BASO, basophil; LUC, large unstained cell; MPV, mean platelet volume; APTT, activated partial thromboplastin time; PT, prothrombin time; Na, sodium; K, potassium; Cl, chloride; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase MB fraction; BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Ca, actual calcium; Mg, magnesium; ABGA, arterial blood gas analysis; BE, base excess; O2CT, oxygen content; O2SAT, oxyhemoglobin saturation; TCO2, total carbon dioxide; CRP, c-reactive protein.

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select a feature subset that has the same discernibility as the original set of features. From the medical viewpoint, this approach aims to identify subsets of the most informative attributes that would influence the treatment of patients. Such rule induction methods generate decision rules, which may potentially reveal profound medical knowledge and provide new medical insight. These rules are more useful for medical experts who seek to analyze and gain understanding of the problem at hand [6]. Since this pioneering study was introduced, various related studies have been performed. Bazan [7] compared RST-based methods with statistical methods, neural networks, decision trees, and decision rules using medical data on several pathologies such as lymphography, breast cancer, and primary tumors. He found that the error rates for RS are not only completely comparable, but are also often significantly lower than those obtained using other techniques. Tsumoto [8] investigated the characteristics of such medical reasoning, and showed that the RS representation of diagnostic models is a useful approach for extracting insightful information from medical databases. Carlin et al. [9], who described the application of RS to diagnose suspected acute appendicitis, found that while the difference between a logistic regression (LR) model and RS was quite small, RS offered the advantage of more explicit decision rules. Komorowski and Øhrn [10] discussed the use of an RS framework to identify a patient group in need of a scintigraphic scan for subsequent modeling. They showed that the identification of such patients has the potential to lower the cost of medical care and to improve its quality because, virtually without any loss of information, fewer patients may be referred for this procedure.

These models offer a common advantage, in that their results are directly interpretable, and the decisions obtained from uncertain, incomplete, or approximate data become explainable for unknown phenomena [11]. However, most of these studies have focused on the issues, the discriminatory power of decision models, or the decision rules derived from different algorithms, but without performing a comparison of the significance of their results. In this study, we describe the scheme of a decision-making model based on rough set and decision tree approaches in order to extract the most relevant factors and knowledge from high-dimensional clinical data that typically incur great extra expense and impose an increased workload on clinicians, and we then apply it to the widespread problem of congestive heart failure (CHF).

2. Methods

2.1. Congestive heart failure data

We retrospectively collected the medical records of all patients who went to the emergency medical center of Keimyung University Dongsan Hospital complaining mainly of dyspnea, between July 2006 and June 2007. Only complete medical records with no missing values were included, i.e., demographic characteristics (age and gender), and clinical laboratory findings, such as urinalysis, common blood cell and differential counts, serum electrolytes, routine admission tests, and arterial blood gas analysis. Patients diagnosed with complaints other than CHF were excluded, such as those who presented evidence such as coronary heart disease, including left ventricular (LV) asynergy or a history of previous coronary bypass surgery, significant congenital or valvular disease, or known cardiomyopathy. Eligibility for the study group ($n = 71$) was defined according to the International Classification of Diseases – 10 codes, I50.0. Discharged patients ($n = 88$), i.e., non-cardiogenic dyspnea (Non-CD) patients who were admitted to the emergency medical center complaining mainly of dyspnea, were defined as the control group. All data collected was reconfirmed by three cardiovascular specialists.

2.2. Statistical analysis

Univariate correlations between clinical features were evaluated using the Chi-square test or Fisher's exact test, which are appropriate for categorical variables, and using the Student t-test or Mann-Whitney U-test with continuous variables, after first checking for normality using the Kolmogorov-Smirnov test. The collected data was expressed as a percentage or mean ± standard deviation. A two-tailed $p < 0.05$ was selected as the level of statistical significance. Following a univariate analysis, a logistic regression (LR) model with Wald's forward feature selection was used for multivariate analysis to identify the independent predictors of CHF, with entry and removal criteria of 0.05 and 0.10 as the default settings. The results are shown as odds ratios (OR) with 95% confidence intervals (95% CI). All statistical analyses were performed using SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

2.3. Selection of reference intervals

Most of the clinical findings, such as laboratory tests and electrocardiogram results are numerical. For a more accurate discriminative diagnosis, evaluation of therapeutic effects, and prognosis, it is necessary to provide an appropriate reference. In laboratory medicine, even though there has been no definition of normal subjects, a normal value is considered to be observed in subjects under normal conditions. Since clinicians evaluate laboratory data or disease conditions in terms of normal values or ranges, normal values are necessary for the interpretation of numerical laboratory data. Most of the normal values or ranges that are commonly used have been statistically calculated from data obtained from a sample population consisting of individuals who are considered normal, or not abnormal, based upon certain criteria [12]. Generally, the standard limits of normal values are between 2.5 and 97.5 centiles, thus defining a 95% reference interval. Normal ranges are used instead of the reference interval, based upon the logic that values outside the range are abnormal. One flaw in this rationale, however, is that by definition, 5% of normal individuals will have values outside the normal range. There is also possible confusion within the normal distribution; modeling the data under the assumption of normality is a common approach but is not always appropriate for the estimation of reference limits [13]. To address these issues, we describe a method for extracting appropriate reference intervals from clinical laboratory data, using the maximum entropy principle (MEP).

The MEP [14] is an unsupervised learning method for determining the classification boundaries, i.e., cut-off points, in various application areas such as pattern classification [15,16] and image processing [17,18]. If we suppose that X is a discrete random variable and the range $R = \{x_1, x_2, \ldots, x_n\}$ is finite or countable and $p_i = P[X = x_i]$, $i = 1, 2, \ldots, n$, then the Shannon entropy of X is defined as

$$H(X) \cong \sum_{i=1}^{n} p_i \log_a \frac{1}{p_i} = -\sum_{i=1}^{n} p_i \log_a p_i \tag{1}$$

Eq. (1) defines the entropy $H(X)$ of the random variable X so that it represents the amount of information contained in X, and includes as a measure of uncertainty the stochastic field of X. $H(X)$ represents its function of probability distribution $p_1, p_2, \ldots, p_n$, and is defined as

$$H(X) = H(p_1, p_2, \ldots, p_n) \cong -\sum_{i=1}^{n} p_i \log p_i \tag{2}$$

If K is a set of the data point values of a random variable, p_i is the probability of the ith histogram level, N is the number of partitions or subspaces of K. Each subspace is denoted as K_j ($j = 1, 2, \ldots, N$), and $p(K_j)$ is denoted as the probability from the cumulative probability $\sum_{j \in K_j} p_j$ of K_j. A thresholding function is then defined as follows.

$$H(K,N) = \sum_{j=1}^{N} \| p(K_j) - 1/N \| \quad (3)$$

Here $\|\cdot\|$ is a norm. As described in [19], if $p(K_j) = 1/N$, then $H(K,N)$ reaches the minimum of 0, and the entropy $H(A)$ of Eq. (2) will reach its maximum. Thus, the MEP-based discretization method is similar to that of equal frequency binning, which operates by fixing a number of intervals N and examining the histogram of each attribute, and $N-1$ cut-off points are determined so that approximately the same number of samples fail into each of the N intervals [11].

In this study, we extracted two threshold values, T_1 and T_2, which satisfy the criteria $\sum_{i=1}^{T_1-1} p(x_i) \cong \sum_{T_1}^{T_2-1} p(x_i) \cong \sum_{T_2}^{n} p(x_i)$, in order to extract the reference intervals $[T_1, T_2)$ of clinical factors, and define the normal range of normal human subjects, i.e., a control group. The data point values in each subspace were converted into three discrete values, which are referred to as low, medium, and high.

2.4. Rough set attribute reduction

RST [2] provides mathematical techniques for creating approximate descriptions of objects or cases, and it has been employed to remove superfluous condition attributes from discrete-valued datasets. Successful examples of this are the rough set attribute reduction methods that use a discernibility matrix and functions [5,20], and dependency or significance measures [3,4,7,21,22]. Among these attribute reduction methods, this study utilizes the concept of a decision-relative discernibility matrix and functions in order to find the subset of the clinical factors associated with CHF predictors. For more details regarding RST, including the concepts of indiscernibility and set approximation, the dependency or significance of attributes, etc., the reader is referred to the literature (See [2,5,23,24]).

In general, a dataset is represented as a table, in which each row represents an object or a case. Every column represents an attribute that can be measured for each object. Such a table is called an information system or table. More formally, it is a pair $\mathbf{A} = (U, A)$, where U is a non-empty set of finite objects, i.e., the universe of discourse, and A is a non-empty finite set of attributes such that a: $U \to V_a$ for every $a \in A$. V_a is the set of values that attribute a may take, and is called the domain of a. In most medical applications, an outcome is known. This *a posteriori* knowledge is expressed as a single distinct attribute, which is called the decision attribute. Information systems of this kind are called decision systems [23,24]. A decision system is any information system of the form $\mathbf{A}^* = (U, A, D)$, where A is the set of condition attributes and D is the set of decision attribute(s) (See Table 1). In the table, there is a universe of six objects, $U = \{x_1, \ldots, x_6\}$, each of which is described by means of four condition attributes: Total bilirubin, Direct bilirubin, Pro BNP, and Troponin I, and one decision attribute, namely Diagnosis.

A decision-relative discernibility matrix of $\mathbf{A}^*$ is a symmetric $n \times n$ matrix, whose entries are defined by

$$c_{ij}^* = \begin{cases} \varnothing, & \text{if and only if } d(x_i) = d(x_j), \\ c_{ij}, & \text{otherwise.} \end{cases}$$

$$\text{where } c_{ij} = \{a \in A : a(x_i) \neq a(x_j)\}, \quad \text{for } i,j = 1, \ldots, n \quad (4)$$

Table 1
Example of a decision system.

U	Total bilirubin	Direct bilirubin	Pro BNP	Troponin I	Diagnosis
1	Medium	Low	High	High	CHF
2	Low	Medium	Medium	Medium	Non-CD
3	High	Low	Low	Medium	CHF
4	Low	Medium	Low	High	Non-CD
5	Low	Low	High	Low	CHF
6	Low	Low	Medium	Low	Non-CD

This only considers those object discernibilities that occur when the corresponding decision values differ. From the example data in Table 1, the decision-relative discernibility matrix in Table 2 was produced. For example, it can be seen from the table that objects 1 and 2 differ in regard to each attribute. Although some attributes in objects 2 and 4 differ (e.g., Pro BNP and Troponin I), their corresponding decisions are the same, so no entry appears in the decision-relative matrix.

A discernibility function $f_{\mathbf{A}^*}$ is a Boolean function of m Boolean variables $a_1^*, \ldots, a_m^*$ that correspond to the attributes $a_1, \ldots, a_m$, which are defined as below:

$$f_{\mathbf{A}^*}(a_1^*, \ldots, a_m^*) = \wedge\{\vee c_{ij}^* | 1 \leqslant j \leqslant i \leqslant n, c_{ij} \neq \varnothing\} \quad (5)$$

where $c_{ij}^* = \{a^* | a \in c_{ij}\}$. By finding the set of all prime implicants of the discernibility function, all the minimal reducts of a system may be determined. From Table 2, the decision-relative discernibility function is defined as:

$$f_{\mathbf{A}^*}(a^*, b^*, c^*, d^*) = (a \vee b \vee c \vee d) \wedge (a \vee b \vee c) \wedge (a \vee c \vee d) \wedge (b \vee c \vee d) \wedge (a \vee b \vee d) \wedge (a \vee c \vee d) \wedge c$$

Further simplification can be obtained by removing those clauses that are subsumed by others:

$$f_{\mathbf{A}^*}(a^*, b^*, c^*, d^*) = (a \vee b \vee d) \wedge c$$

The set of all prime implicants of $f_{\mathbf{A}^*}(a^*, b^*, c^*, d^*)$ is $\{a, c\}$, $\{b, c\}$, or $\{c, d\}$. Therefore, there are three decision-relative reducts, namely {Total bilirubin, Pro BNP}, {Direct bilirubin, Pro BNP}, and {Pro BNP, Troponin I} that can be used to distinguish between a diagnosis of CHF and Non-CD, with {Pro BNP} as a core, i.e., an indispensable predictor, in the decision system. In a high-dimensional dataset, the finding of all possible decision-relative reducts is a non-deterministic polynomial-time hard (NP-hard) problem. Obviously then, the calculation of all reducts is very complex, but in many practical applications all the reducts do not need to be calculated, but only some of them.

To address this issue, we used Johnson's reduction algorithm in order to find a single reduct without exhaustively generating all possible reducts, which offer no guarantee of minimality but are generally of a size close to the minimal. The algorithm begins by setting the current reduct candidate to the empty set. Each condition attribute appearing in the discernibility function is then evaluated according to a heuristic measure. For the standard Johnson reduction algorithm, this is typically a count of the number of appearances of an attribute within clauses. The attribute that has the highest heuristic value is added to the candidate reduct, and all clauses in the discernibility function that contain this attribute are removed. As soon as all clauses have been removed, the algorithm terminates and returns the reduct [5]. For more details, the reader is referred to the literature (See [25,26]).

In this way, we investigated decision-relative reducts that were extracted from each training dataset during k-fold cross-validation (in our study, $k = 10$), and we then utilized these to construct a scheme for a decision-making model (Fig. 1) using the C5.0

Table 2
Decision-relative discernibility matrix of Table 1.

c_{ij}^*	1	2	3	4	5	6
1	Ø	{a,b,c, d}	Ø	{a,b,c}	Ø	{a,c,d}
2	{a,b,c,d}	Ø	{a,b,c}	Ø	{b,c,d}	Ø
3	Ø	{a,b,c}	Ø	{a,b,d}	Ø	{a,c,d}
4	{a,b,c}	Ø	{a,b,d}	Ø	{b,c,d}	Ø
5	Ø	{b,c,d}	Ø	{b,c,d}	Ø	{c}
6	{a,c,d}	Ø	{a,c,d}	Ø	{c}	Ø

a: Total bilirubin; b: Direct bilirubin; c: Pro BNP; d: Troponin I.

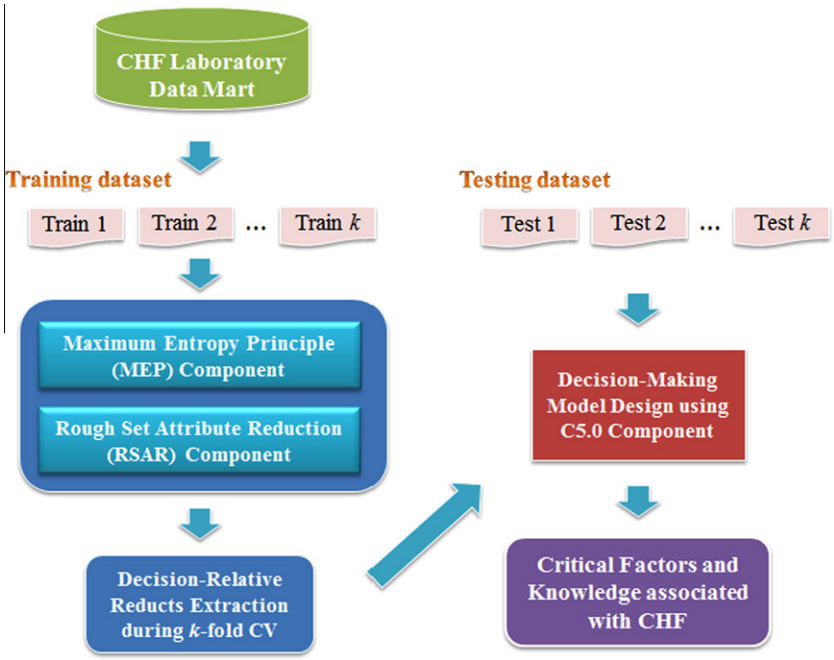

Fig. 1. Scheme of decision-making model.

decision tree algorithm in Clementine version 12.0 (SPSS Inc., Chicago, IL, USA). Here, the MEP and RSAR components were implemented on MATLAB version 2010b.

2.5. Evaluation of decision-making models

We used 10-fold cross-validation (CV) experiments to provide an unbiased estimate of the generalization error. The full dataset was randomly divided into 10 subsets:9 subsets were used for training (90%), and the remaining subset was used for testing (10%). The process was then repeated 10 times. The performance of the models was evaluated using six standard measures, accuracy (ACC), sensitivity (SENS), specificity (SPEC), positive predictive value (PPV), negative predictive value (NPV), and the area under the ROC curve (AUC). A confusion matrix contains information, i.e., difference, about actual and predicted outcomes done by a classification system. Table 3 shows the confusion matrix for a binary classification problem. Then the five measures can be defined by using the elements of the confusion matrix as

$$ACC = \frac{TP + TN}{TP + FN + TN + FP} \times 100 \quad (6)$$

$$SENS = \frac{TP}{TP + FN} \times 100 \quad (7)$$

$$SPEC = \frac{TN}{TN + FP} \times 100 \quad (8)$$

$$PPV = \frac{TP}{TP + FP} \times 100 \quad (9)$$

$$NPV = \frac{TN}{TN + FN} \times 100 \quad (10)$$

Table 3
Confusion matrix.

	Predicted outcome	
	Positive (e.g., CHF)	Negative (e.g., Non-CD)
Actual outcome		
Positive (e.g., CHF)	True positive (TP)	False Negative (FN)
Negative (e.g., Non-CD)	False Positive (FP)	True Negative (TN)

where TP and TN are the correctly classified positives and negatives, FP and FN are the incorrectly classified positives and negatives. Next, the AUC was used to measure how well a decision model performed, i.e., a trade-off between sensitivity and specificity [27]. We also made a pairwise comparison [28] between the ROC curves of the models in order to test for statistically significant differences.

3. Experimental results

3.1. Univariate and multivariate analysis

There were significant differences between patients with CHF (mean age, 73.4 ± 9.9 years) and those with Non-CD (mean age, 65.2 ± 15.1 years), in terms of age ($p < 0.001$); gender ($p < 0.05$); and the urinalysis results for OB ($p < 0.05$) and RBC ($p < 0.01$), as listed in Table 4. The clinical findings for the common blood cell and differential count, serum electrolytes, routine admission, arterial blood gas analysis, etc. showed that the following were significantly or slightly higher in patients with CHF: MCV ($p < 0.05$), MPV ($p < 0.001$), APTT ($p < 0.05$), PT ($p < 0.001$), K ($p < 0.01$), LDH ($p < 0.01$), CK-MB ($p < 0.001$), Inorganic Phosphorus ($p < 0.001$), BUN ($p < 0.001$), Creatinine ($p < 0.001$), Total bilirubin ($p < 0.01$), Direct bilirubin ($p < 0.01$), ALP ($p < 0.05$), AST ($p < 0.01$), Mg ($p < 0.01$), Pro BNP ($p < 0.001$), and Troponin I ($p < 0.001$). In contrast, the following were slightly higher in patients with Non-CD: RBC ($p < 0.05$), HGB ($p < 0.05$), MCHC ($p < 0.001$), O2CT ($p < 0.05$), O2SAT ($p < 0.05$), and HB ($p < 0.05$). The remaining variables could not be used to differentiate CHF from Non-CD, as can be inferred from Table 5.

In the multivariate analysis, independent risk factors were identified using Wald forward LR to define entry and removal criteria of 0.05 and 0.10. We included four variables in the final LR model that were independently related to CHF (See Table 6): Gender ($p = 0.011$; OR, 3.287; 95% CI, 1.309–8.257), MCHC ($p = 0.052$; OR, 0.696; 95% CI, 0.483–1.003), Direct bilirubin ($p = 0.006$; OR, 25.151; 95% CI, 2.581–245.095), and Pro BNP ($p = 0.000$; OR, 2.156; 95% CI, 1.664–2.793). These variables were tested by linear

Table 4
Comparison of patient characteristics (age, gender, and urinalysis) for patients with congestive heart failure versus non-cardiogenic dyspnea.

Variable	CHF (n = 71)	Control (n = 88)	p Value
Age, yrs	73.39 ± 9.86	65.23 ± 15.14	**<0.000**[a]
Gender			**<0.025**
Male	26 (36.6%)	49 (55.7%)	
Female	45 (63.4%)	39 (44.3%)	
Urinalysis			
Color			0.788
Amber	3 (4.2%)	3 (3.4%)	
Straw	68 (95.8%)	85 (96.6%)	
SG	1.02 ± 0.01	1.02 ± 0.01	0.812
pH	6.08 ± 0.94	6.34 ± 0.87	0.075
Albumin			0.055
Negative	45 (63.4%)	68 (77.3%)	
Positive	26 (36.6%)	20 (22.7%)	
Glucose			0.494
Negative	55 (77.5%)	64 (72.7%)	
Positive	16 (22.5%)	24 (27.3%)	
Ketone			0.703
Negative	65 (91.5%)	79 (89.8%)	
Positive	6 (8.5%)	9 (10.2%)	
OB			**<0.043**
Negative	33 (46.5%)	55 (62.5%)	
Positive	38 (53.5%)	33 (37.5%)	
Urobilinogen, EU/dL	0.30 ± 0.80	0.40 ± 1.16	0.863
Bilirubin			0.956
Negative	66 (93.0%)	82 (93.2%)	
Positive	5 (7.0%)	6 (6.8%)	
Nitrite			0.497
Negative	67 (94.4%)	85 (96.6%)	
Positive	4 (5.6%)	3 (3.4%)	
WBC1			0.135
Negative	51 (71.8%)	72 (81.8%)	
Positive	20 (28.2%)	16 (18.2%)	
RBC			**<0.005**
Negative	13 (18.3%)	34 (38.6%)	
Positive	58 (81.7%)	54 (61.4%)	
WBC2			0.154
Negative	3 (4.2%)	9 (10.2%)	
Positive	68 (95.8%)	79 (89.8%)	
Ep.Cell			0.725
Negative	17 (23.9%)	19 (21.6%)	
Positive	54 (76.1%)	69 (78.4%)	
Cast			–
Negative	71 (100.0%)	88 (100.0%)	
Positive	–	–	
Other			0.755
Negative	67 (94.4%)	84 (95.5%)	
Positive	4 (5.6%)	4 (4.5%)	
Crystal			0.368
Negative	71 (100.0%)	87 (98.9%)	
Positive	–	1 (1.1%)	

[a] Mann-Whitney *U*-test.

Table 5
Comparison of patient characteristics (CBC and differential count, serum electrolytes, routine admission, etc.) for patients with congestive heart failure versus non-cardiogenic dyspnea.

Variable	CHF (n = 71)	Control (n = 88)	p Value
CBC and differential count			
WBC, $\times 10^3/\mu$L	9.12 ± 3.62	9.42 ± 4.12	0.846
RBC, $\times 10^3/\mu$L	3.98 ± 0.63	4.21 ± 0.63	<0.025[b]
HGB, g/dL	12.16 ± 2.19	12.87 ± 2.01	<0.034[b]
HCT, %	36.31 ± 6.41	37.53 ± 5.58	0.203
MCV, fl	91.23 ± 5.88	89.34 ± 5.50	<0.039[b]
MCH, pg	30.67 ± 2.42	30.79 ± 2.12	0.742
MCHC, g/dL	33.73 ± 1.31	34.52 ± 1.18	<0.000[b]
PLT, $\times 10^3/\mu$L	255.39 ± 109.83	281.06 ± 103.03	0.132
NEUT, %	73.08 ± 11.77	71.96 ± 14.48	0.592
LYMP, %	20.00 ± 11.10	19.38 ± 12.93	0.749
MONO, %	5.14 ± 2.33	5.32 ± 2.27	0.626
EOS, %	2.80 ± 3.57	2.91 ± 3.52	0.213
BASO, %	0.57 ± 0.33	0.54 ± 0.38	0.299
LUC, %	1.85 ± 0.89	1.67 ± 0.76	0.368
MPV, fl	8.43 ± 1.05	7.89 ± 0.80	<0.000[a]
APTT, s	32.05 ± 8.66	29.25 ± 5.28	<0.025[a]
PT, s	1.19 ± 0.35	1.05 ± 0.22	<0.000[a]
Fibrinogen, mg/dL	348.25 ± 90.68	379.71 ± 111.72	0.052
Serum electrolytes			
Na, mmol/L	142.61 ± 6.02	142.72 ± 4.88	0.333
K, mmol/L	4.75 ± 0.93	4.36 ± 0.57	<0.009[a]
Cl, mmol/L	105.62 ± 7.48	105.30 ± 5.18	0.177
LDH, U/L	740.87 ± 466.11	571.55 ± 172.63	<0.002[a]
Lipase, U/L	31.97 ± 17.47	30.52 ± 16.53	0.752
CK, U/L	163.55 ± 150.15	201.83 ± 283.56	0.581
CK-MB, ng/mL	3.67 ± 4.78	2.43 ± 3.53	<0.000[a]
Amylase, U/L	50.10 ± 27.52	47.98 ± 21.36	0.770
Routine admission			
Total calcium, mg/dL	8.74 ± 0.60	8.90 ± 0.67	0.118
Inorganic phosphorus, mg/dL	4.08 ± 1.19	3.34 ± 0.82	<0.000[b]
Glucose, mg/dL	174.38 ± 78.27	156.08 ± 60.56	0.129
BUN, mg/dL	30.83 ± 21.37	19.60 ± 13.53	<0.000[a]
Creatinine, mg/dL	1.62 ± 1.07	1.14 ± 0.72	<0.000[a]
Cholesterol, mg/dL	172.61 ± 48.65	168.66 ± 43.71	0.591
Total protein, g/dL	6.85 ± 0.69	6.91 ± 0.72	0.632
Albumin, g/dL	3.82 ± 0.36	3.89 ± 0.44	0.316
Total bilirubin, mg/dL	1.04 ± 0.71	0.73 ± 0.39	<0.002[a]
Direct bilirubin, mg/dL	0.37 ± 0.25	0.26 ± 0.17	<0.001[a]
ALP, U/L	100.24 ± 31.94	94.74 ± 47.48	<0.038[a]
AST, U/L	106.80 ± 231.56	41.33 ± 67.67	<0.008[a]
ALT, U/L	71.58 ± 152.29	30.52 ± 30.66	0.348
Ca, mEq/L	2.25 ± 0.15	2.29 ± 0.16	0.061
Mg, mg/dL	2.33 ± 0.35	2.16 ± 0.30	<0.003[a]
ABGA			
pH	7.46 ± 0.06	7.46 ± 0.07	0.977
pCo2, mmHg	38.47 ± 13.29	38.56 ± 10.68	0.176
pO2, mmHg	77.64 ± 14.69	83.11 ± 19.77	0.054
HCo3, mmol/L	29.96 ± 5.20	25.16 ± 4.08	0.105
BE, mmol/L	-0.26 ± 5.67	1.47 ± 3.35	0.060
O2CT, Vol%	14.74 ± 3.58	16.36 ± 3.26	<0.010[a]
O2SAT, mmHg	95.88 ± 2.85	96.75 ± 2.03	<0.031[b]
TCo2, mmol/L	25.06 ± 5.46	26.33 ± 4.36	0.106
HB, g/dL	11.62 ± 2.48	12.43 ± 2.27	<0.033[b]
HCT	35.84 ± 7.12	37.75 ± 6.53	0.080
CRP, mg/dL	1.77 ± 2.12	4.15 ± 6.08	0.184
Pro BNP[c], pg/mL	8.65 ± 1.45	5.77 ± 2.08	<0.000[a]
Troponin I, ng/mL	0.42 ± 1.20	0.11 ± 0.20	<0.000[a]

[a] Mann-Whitney *U*-test.
[b] Student *t*-test.
[c] Log-transformed.

regression analysis in order to evaluate the possible problem of multicollinearity, which occurs when two or more predictors in a model are correlated. The data did not violate the assumption of multicollinearity, as the tolerance of each independent variable was greater than 0.883. The variance inflation factor (VIF) values of the variables ranged from 1.096 to 1.132. The performance of five standard measures, ACC, SENS, SPEC, PPV, and NPV was 79.9%, 78.9%, 80.7%, 76.7%, and 82.6%, respectively. The AUC of the LR model was 79.8% (95% CI, 0.727–0.857), which indicates a fair degree of discriminatory power.

3.2. LR-based decision-making model versus RS-based decision-making model

Based upon the independent predictors in Table 6, we constructed a decision-making model using the C5.0 decision tree model. The LR-based decision model is shown in Fig. 2, and eight decision rules were generated from the full dataset. Cases were categorized based upon the criteria of the decision rules. After applying Fisher's exact tests, the following four rules associated with CHF in the LR-based decision model were found to be statistically significant:

Table 6
Multivariate analysis of predictors of CHF.

Variable	Coefficient (β)	Standard error	OR	95% CI	*p* Value
Gender	1.190	0.470	3.287	1.309–8.257	0.011
MCHC	−0.363	0.186	0.696	0.483–1.003	0.052
Direct bilirubin	3.225	1.162	25.151	2.581–245.095	0.006
Pro BNP[a]	0.768	0.132	2.156	1.664–2.793	0.000
Intercept	3.673	6.475	39.361	–	0.571

OR: odd ratios; $R^2 = 0.434$; $n = 159$.
[a] Log-transformed.

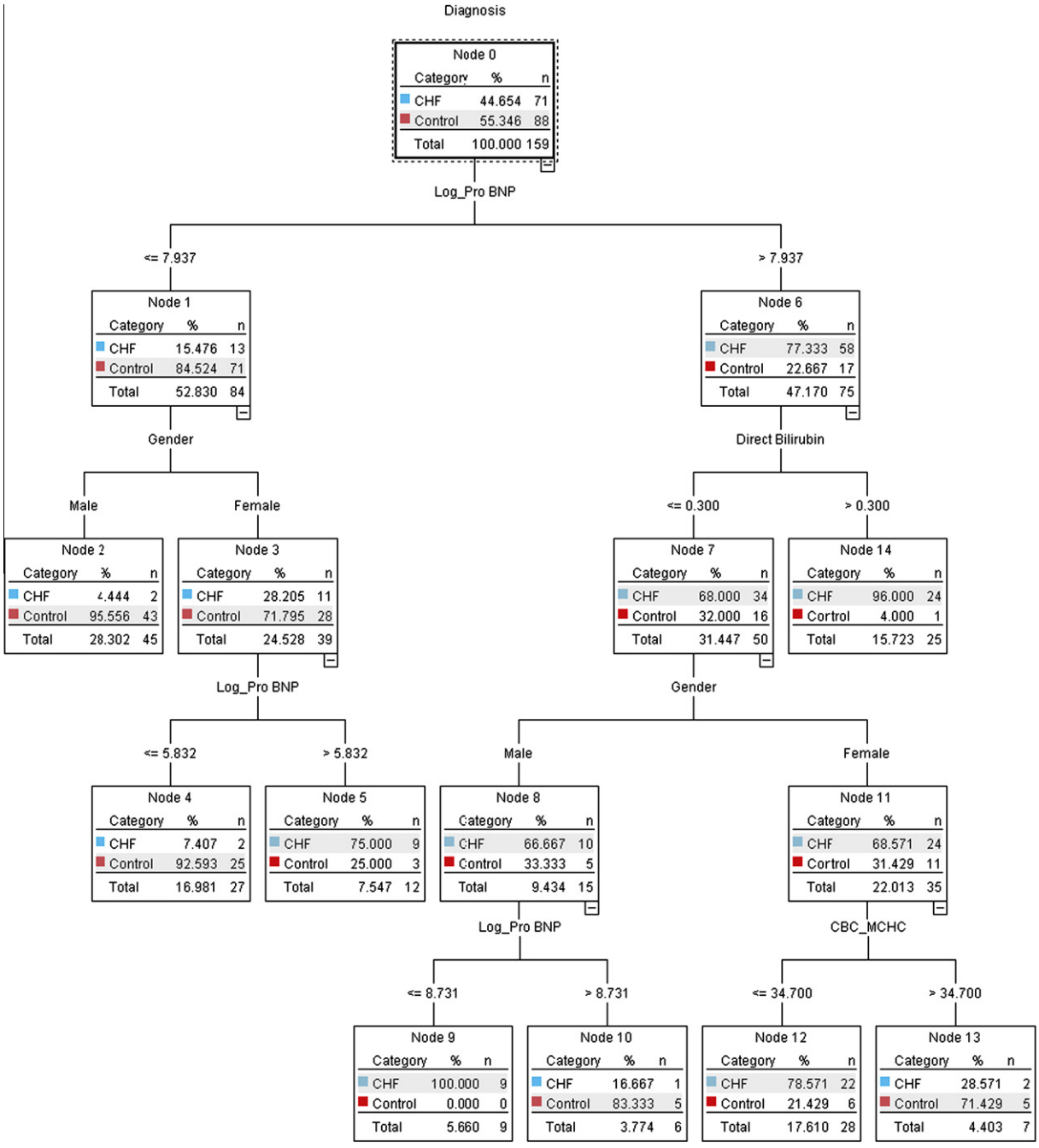

Fig. 2. LR-based decision-making model.

(1) IF Pro BNP > 7.94 pg/mL AND Direct bilirubin > 0.3 mg/dL, THEN the Diagnosis is CHF ($p < 0.01$).

(2) IF Pro BNP $\leqslant$ 7.94 pg/mL AND Female AND Pro BNP > 5.83 pg/mL, THEN the Diagnosis is CHF ($p < 0.001$).

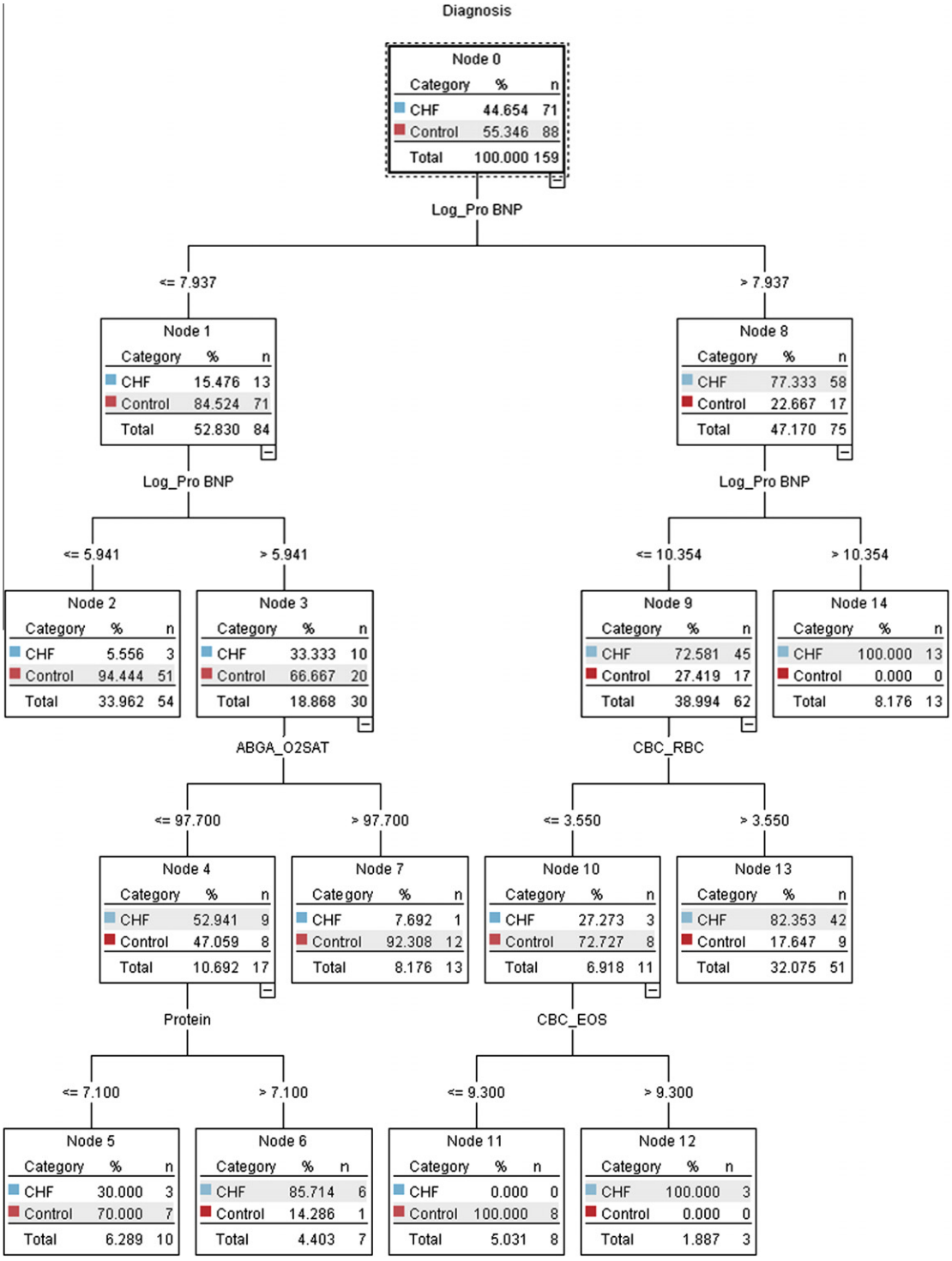

Fig. 3. RS-based decision-making model.

(3) IF Pro BNP > 7.94 pg/mL AND Direct bilirubin ⩽ 0.3 mg/dL AND Male AND Pro BNP ⩽ 8.73 pg/mL, THEN the Diagnosis is CHF ($p < 0.01$).
(4) IF Pro BNP > 7.94 pg/mL AND Direct bilirubin ⩽ 0.3 mg/dL AND Female AND MCHC ⩽ 34.7 g/dL, THEN the Diagnosis is CHF ($p < 0.05$).

In the proposed model, a decision-relative reduct was selected using the RSAR component: {RBC, HCT, EOS, MPV, Protein, O2SAT, Pro BNP}. Then the differences in the references as calculated using the MEP component were as follows:

- **Non-CD (control group)**

  RBC: [3.83, 4.65); HCT: [33.1, 41.2); EOS: [1.0, 3.0); MPV: [7.3, 8.2); Protein: [6.3, 7.2); O2SAT: [95.7, 98.2); Pro BNP: [4.12, 7.47)

- **CHF**

  RBC: [3.62, 4.36); HCT: [31.5, 41.1); EOS: [0.5, 3.4); MPV: [7.8, 8.6); Protein: [6.3, 7.2); O2SAT: [94.4, 98.1); Pro BNP: [8.08, 9.77)

Table 7
Decision-relative reducts selected from RSAR component during 10-fold cross validation.

	Variable	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	Frequency
	Age	•	•	•								3
Urinalysis	SG					•					•	2
	Glucose				•							1
	WBC1							•				1
CBC and differential count	RBC		•									1
	HGB						•					1
	HCT	•				•		•	•	•	•	6
	MCV			•			•					2
	MCHC	•			•	•	•		•	•	•	7
	PLT	•										1
	MONO				•							1
	EOS	•			•					•	•	4
	MPV					•						1
	APTT		•				•					2
	Fibrinogen									•		1
Serum electrolytes	Na				•							1
	Cl		•									1
	LDH	•										1
	Lipase			•								1
	Amylase		•									1
Routine admission	Inorganic phosphorus	•				•			•			3
	Cholesterol									•		1
	Albumin							•				1
	ALP						•					1
	AST							•	•			2
	Ca			•				•	•	•	•	5
	Mg		•									1
ABGA	pH					•						1
	O2SAT			•			•					2
	Pro BNP	•	•	•	•	•	•	•	•	•	•	10

From these results, we confirmed that the reference of Pro BNP was remarkably different in the lower and upper limits, and the clinical factor EOS was different in the lower limit. Based upon the reduct, we constructed a decision-making model using the same method as was used in the previous experiment. After the application of a C5.0 decision tree approach, five clinical factors {RBC, EOS, Protein, O2SAT, Pro BNP} of the decision-relative reduct were determined in order to generate the decision rules associated with CHF. The RS-based decision model is shown in Fig. 3, and the following four rules were found to be statistically significant:

(1) IF Pro BNP > 7.937 pg/mL AND Pro BNP > 10.354 pg/mL, THEN the Diagnosis is CHF ($p < 0.05$).
(2) IF Pro BNP > 7.937 pg/mL AND Pro BNP $\leqslant$ 10.354 pg/mL AND RBC > 3.55 $10^3/\mu$L, THEN the Diagnosis is CHF ($p < 0.001$).
(3) IF Pro BNP $\leqslant$ 7.937 pg/mL AND Pro BNP > 5.941 pg/mL AND O2SAT $\leqslant$ 97.7 mmHg AND Protein > 7.1 g/dL, THEN the Diagnosis is CHF ($p < 0.05$).
(4) IF Pro BNP > 7.937 pg/mL AND Pro BNP $\leqslant$ 10.354 pg/mL AND RBC $\leqslant$ 3.55 $10^3/\mu$L AND EOS > 9.3%, THEN the Diagnosis is CHF ($p < 0.01$).

Table 7 shows the decision-relative reducts that were extracted from 10 training datasets during the 10-fold CV. The leftmost column consists of clinical laboratory tests; the 2nd column lists test names; the 3rd–12th columns denote folds, where the symbol • represents the reducts selected using the RSAR component for each training dataset; and the rightmost column denotes the occurrence frequency of corresponding clinical factors. The references, which were defined as the minimum and maximum values of the lower and upper limits of the clinical factors, were determined as follows:

- **Non-CD (control group)**
  Age: [55, 76); Urine SG: [1.005, 1.015); RBC: [3.77, 4.71); HGB: [11.3, 14.6); HCT: [33.0, 41.8); MCV: [85.6, 93.3); MCHC: [33.5, 35.5); PLT: [203, 347); MONO: [3.5, 6.9)
  EOS: [0.9, 3.4); MPV: [7.3, 8.2); Na: [139, 144); Cl: [102, 108)
  Inorganic phosphorus: [2.8, 3.8); Cholesterol: [138, 205); Albumin: [3.5, 4.1); ALP: [69, 103); AST: [20, 41); pH: [7.427, 7.488); O2SAT: [95.5, 98.3); APTT: [25.4, 31.9); Fibrinogen: [289.6, 477.2); LDH: [442, 669); Lipase: [19, 36); Amylase: [32, 58)
  Ca: [2.19, 2.35); Mg: [1.9, 2.2); Pro BNP: [4.10, 7.91)
- **CHF**
  Age: [66, 80); Urine SG: [1.005, 1.015); RBC: [3.59, 4.42); HGB: [10.1, 14.0); HCT: [31.4, 41.4); MCV: [87.0, 94.7); MCHC: [32.6, 34.6); PLT: [176, 325); MONO: [3.2, 6.5)
  EOS: [0.5, 3.6); MPV: [7.7, 8.9); Na: [139, 145); Cl: [100, 110); Inorganic phosphorus: [3.1, 4.8)
  Cholesterol: [128, 211); Albumin: [3.5, 4.0); ALP: [72, 121); AST: [24, 86); pH: [7.421, 7.508)
  O2SAT: [94.3, 98.2); APTT: [26.5, 34.5); Fibrinogen: [285.6, 416.3); LDH: [493, 824)
  Lipase: [19, 38); Amylase: [27, 62); Ca: [2.14, 2.34); Mg: [2.0, 2.4); Pro BNP: [8.01, 9.93)

Table 8 shows the results of a comparison of the six performance measures used in the LR-based and RS based decision-making models, in which the RS-based decision model was constructed from clinical factors that were selected while the criteria of the occurrence frequency were adjusted between 1 and 10. When the criteria were defined as 2 or 3, 4 or 5, and 7–10, the performance of the models was the same, regardless of the number of features, prior to the application of the C5.0 decision tree component. These

Table 8
Comparisons of performance of decision support models during 10-fold cross validation.

Model	ACC	SENS	SPEC	PPV	NPV	AUC	No. rules
LR-based decision tree model	88.7 (SD 3.2)	90.1 (SD 2.8)	87.5 (SD 5.7)	85.3 (SD 5.9)	91.7 (SD 2.5)	88.8 (SD 3.1)	8
RS-based decision tree model (over 1)	97.5 (SD 1.1)	97.2 (SD 1.7)	97.7 (SD 1.6)	97.2 (SD 2.1)	97.7 (SD 1.4)	97.5 (SD 1.1)	18
RS-based decision tree model (over 2 or 3)	83.0 (SD 3.0)	90.1 (SD 4.2)	77.3 (SD 4.3)	76.2 (SD 3.8)	90.7 (SD 3.8)	83.7 (SD 3.0)	4
RS-based decision tree model (over 4 or 5)	87.4 (SD 3.1)	90.1 (SD 4.1)	85.2 (SD 3.8)	83.1 (SD 5.1)	91.5 (SD 3.9)	87.7 (SD 3.2)	8
RS-based decision tree model (over 6)	83.0 (SD 3.1)	81.7 (SD 3.8)	84.1 (SD 4.3)	80.6 (SD 6.6)	85.1 (SD 2.6)	82.9 (SD 3.0)	5
RS-based decision tree model (over 7–10)	80.5 (SD 3.0)	81.7 (SD 3.8)	79.5 (SD 4.5)	76.3 (SD 3.0)	84.3 (SD 3.8)	80.6 (SD 3.0)	2

Six measures, ACC, SENS, SPEC, PPV, NPV, and AUC (mean and SD) show test performance from 10 trials, where 90% of the dataset were used for training and 10% for testing.

Table 9
Pairwise comparison between the ROC curves of different decision support models.

Model	LR-based decision tree model	RS-based decision tree model (over 1)	RS-based decision tree model (over 2 or 3)	RS-based decision tree model (over 4 or 5)	RS-based decision tree model (over 6)	RS-based decision tree model (over 7–10)
LR-based decision tree model	–	$p = 0.005$[a] (95% CI: 2.63–14.6)	$p = 0.120$ (95% CI: −1.33–11.6)	$p = 0.716$ (95% CI: −4.99–7.26)	$p = 0.097$ (95% CI: −1.07–12.9)	$p = 0.030$[a] (95% CI: 0.81–15.6)
RS-based decision tree model (over 1)	$p = 0.005$[a] (95% CI: 2.63–14.6)	–	$p < 0.000$[a] (95% CI: 7.08–20.4)	$p = 0.001$[a] (95% CI: 3.78–15.8)	$p < 0.000$[a] (95% CI: 7.91–21.2)	$p < 0.000$[a] (95% CI: 9.86–23.8)
RS-based decision tree model (over 2 or 3)	$p = 0.120$ (95% CI: −1.33–11.6)	$p < 0.000$[a] (95% CI: 7.08–20.4)	–	$p = 0.027$[a] (95% CI: 0.45–7.51)	$p = 0.759$ (95% CI: −4.40–6.03)	$p = 0.189$ (95% CI: −1.52–7.70)
RS-based decision tree model (over 4 or 5)	$p = 0.716$ (95% CI: −4.99–7.26)	$p = 0.001$[a] (95% CI: 3.78–15.8)	$p = 0.027$[a] (95% CI: 0.45–7.51)	–	$p = 0.069$ (95% CI: −0.38–9.97)	$p = 0.017$[a] (95% CI: 1.28–12.9)
RS-based decision tree model (over 6)	$p = 0.097$ (95% CI: −1.07–12.9)	$p < 0.000$[a] (95% CI: 7.91–21.2)	$p = 0.759$ (95% CI: −4.40–6.03)	$p = 0.069$ (95% CI: −0.38–9.97)	–	$p = 0.140$ (95% CI: −0.75–5.29)
RS-based decision tree model (over 7–10)	$p = 0.030$[a] (95% CI: 0.81–15.6)	$p < 0.000$[a] (95% CI: 9.86–23.8)	$p = 0.189$ (95% CI: −1.52–7.70)	$p = 0.017$[a] (95% CI: 1.28–12.9)	$p = 0.140$ (95% CI: −0.75–5.29)	–

[a] Pairwise comparison between ROC curves indicated statistically significant difference.

results indicate that the features selected by the RS-based decision model (over 1) are able to produce a classifier with a larger AUC than that selected by the LR-based decision model using Gender, MCHC, Direct bilirubin, and Pro BNP, while the RS-based decision model results (over 4 or 5) for AUC were similar.

To describe the pairwise comparison between the ROC curves of the models, we also investigated the discriminatory capabilities of six models; the results are presented in Table 9. From these results, we can see that as a feature pre-selection approach, the RS-based decision model (over 1) had significantly better discriminatory power than the decision model with LR.

4. Discussion and conclusion

One of the most difficult problems faced in medical practice is distinguishing patients experiencing heart failure from those with dyspnea. To address this issue, this study presented a scheme for a decision-making model based on RST and decision tree approaches. The scheme's goal is to extract the most relevant factors and their references, and to identify decision rules for early diagnosis in patients with suspected CHF, since they are expensive to process and impose a greater workload upon clinicians. From a full dataset, we extracted features from the RSAR component (RBC, HCT, EOS, MPV, Protein, O2SAT, and Pro BNP as a decision-relative reduct) and from the LR (Gender, MCHC, Direct bilirubin, and Pro BNP as an independent risk factor) that are indispensable to obtaining early diagnostic knowledge of CHF patients. In particular, we identified the risk factor Pro BNP, which was consistent with findings described in previous research articles. Pro BNP is an incremental and independent predictor of increased long-term cardiovascular mortality risk, in addition to clinical risk factors [29]. A change in the level of Pro BNP was the strongest predictor of cardiac outcome, indicating a threefold increase in the risk of a long-term cardiac event [30]. The Pro BNP level may also serve as a useful clinical biomarker when its value is obtained at admission from an unselected patient population following hospitalization for chest pain and potential acute coronary syndrome (ACS). It may also provide complementary prognostic information that can help to establish risk determinants during long-term follow-up [31].

To demonstrate the usefulness of the proposed model, we compared the discriminatory power of decision-making models that utilize RS- and LR-based decision models during 10-fold CV. The experimental results showed that the RS-based decision model (over 1) with all decision-relative reducts (See Table 7) was more effective at distinguishing patients with CHF from those with dyspnea, whereas the LR-based decision model with several independent predictors was less accurate for the test data. In the results, the range of AUC for the RS-based model was approximately 97.5 ± 1.1%, as compared with a range of 88.8 ± 3.1% for the LR-based decision model. There are several explanations for the better results that were obtained, which can be summarized as follows. In the LR-based decision model, the LR analysis can easily scale up to high-dimensional data and are computationally fast and independent of the learning algorithm. The dependence among features, however, is ignored. In the proposed method, on the other hand, the RSAR method, as a feature pre-selection approach, provides a

high probability of producing a model with better classification performance than the LR analysis, by considering the feature dependencies and their collective contribution [27].

This study has the following limitations. The assessment of clinical factors was based on a data set that contained no information regarding clinical histories, symptoms, or electrocardiogram results. The number of patients with CHF and with Non-CD was relatively small, a fact that produced variations when determining the risk factors and decision rules. While it proved to be valid in our cross-validation experiments and was statistically significant, the evidence of the derived rules was verified using an external validation study or prospective study. In addition, the data discretization method (i.e., MEP) that was used as a step in the construction of reference intervals in the proposed model is not specific to the RS approach. However, real-value attributes had to be discretized for the RSAR component, which may have resulted in some loss of information. An alternative solution could be a fuzzy-rough feature selection method [5,21] that reduces dimensions with minimal loss of information. These considerations provide directions that could be fruitful for further research.

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