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DESIGN OF A CLINICAL DECISION SUPPORT FOR DETERMINING VENTILATOR WEANING USING SUPPORT VECTOR MACHINE

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Abstract. *Ventilator weaning is the process of discontinuing mechanical ventilators from patients with respiratory failure. This study designed a clinical decision support system (CDSS) using support vector machine (SVM) to predict if a patient can be weaned from mechanical ventilator successfully. A filter method based on logistic regression analysis (LRA) and a wrapper method based on recursive feature elimination (RFE) were adopted to select salient features in 27 variables, including demographic information, physiology and disease factors, and care and treatment factors for CDSS. Data of 348 patients were collected at four different periods from all-purpose respiratory care center. Seven significant variables ($p < 0.05$) using LRA contrasted to eleven variables using RFE algorithm were selected. The predictive accuracy under cross-validation is 88.33% (LRA) and 92.73% (RFE), respectively. The systems outperform predictors (75-78%) built using frequency-to-tidal volume ratio (f/V_T) and a model (78.6%) constructed recently using a combination of sample entropy of inspiratory tidal volume (VTI), expiratory tidal volume (VTE), and respiration rate (RR). The CDSS constructed using SVM was shown to have better accuracy (91.25%) than using neural network (88.69%). Additionally, the designed CDSS with a graphic user interface (GUI) provides a valuable tool to assist physicians to determine if a patient is ready to wean from the ventilator.*
Keywords: Ventilation weaning, Clinical decision support system, Neural network, Support vector machine, Recursive feature elimination, Logistic regression analysis

1. **Introduction.** In the daily practice of an intensive care unit (ICU), weaning is typically regarded as the whole process of discontinuing mechanical ventilation. Among the ICU patients, 39%-40% need mechanical ventilator for sustaining their lives [1], of which 90% of the patients can be weaned from the ventilator within a few days [2], while other patients need longer ventilator support [3,4]. Ventilator support should be withdrawn promptly when it is no longer necessary so as to reduce the likelihood of known nosocomial complications and costs [5,6].

Because prolonged use of ventilator can have great risks of subglottic injury, respiratory infections, and chronic lung disease [7], discontinuing mechanical ventilation and removing the artificial airway as soon as possible reduce the risk of ventilator-induced lung injury (VILI), nosocomial pneumonia, airway trauma from the endotracheal tube, and unnecessary sedation. However, premature ventilator-discontinuation or extubation can cause respiratory muscle fatigue, gas exchange failure, loss of airway protection, and an increase of patient mortality [8-10]. Therefore, catching the correct time to begin weaning process is very important but difficult in clinical practice.

The rate of successful weaning reached only 35-60% [11-13] if the decisions were made by physicians. Therefore, it is desirable to have objective measurements and weaning predictors that decrease dependence on the knowledge, experience, and skill of individual physicians whose judgments are prone to be unreliable. A clinical decision support system is expected to be able to effectively identify the earliest time of ventilator weaning for a patient to resume and sustain spontaneous breathing, so that unnecessary prolongation of ventilator use can be avoided. By identifying patients who are likely to fail a trial of spontaneous breathing, such indices can prevent a premature weaning attempt and the development of severe cardiorespiratory and/or physiological decompensation.

Several physiological indices, such as rapid shallow breathing index measures by frequency-to-tidal volume ratio (f/V_T), maximal inspiration pressure (PImax), vital capacity (VC), minute ventilation (VE), pH and pCO2 values of stomach mucosa, arterial blood gas levels, fraction of inspired oxygen, alveolar-arterial oxygen pressure difference (A-a gradient), blood urine nitrogen (BUN) level, serum creatinine level, and serum albumin level, have been reported to be useful for weaning prediction [14-20]. However, no agreement has been made so far to determine which indices should be monitored [12,13]. In addition, previous studies only focused on physiological variables, while other factors including diseases, for example, pulmonary, cardiac, respiratory and brain vessel diseases, and therapeutic progression indexes, such as acute physiology and chronic health evaluation II (APACHE II) and coma scales, were seldom considered. Predictors designed using indices obtained from a single device tend to incur systematic errors [21]. Hence, adoption of multiple indices obtained from various modalities is useful in eliminating systematic errors. Furthermore, some of these indices, such as pH and pCO2 values of stomach mucosa, are not easy to measure clinically and not widely adopted in ICU for assessing ventilator weaning. APACHE II is a classification system for evaluating disease severity for a patient based on 12 routine physiological tests [22]. A higher score implies more severe disease and high risk of death. Galsgow coma scale, on the other hand, aims at objectively evaluating the conscious state of a patient based on the neurological status. The scale spans a range from 3 to 15 points with a smaller point indicating deeper unconsciousness for a patient.

As mentioned above, the main shortcoming of the existing results is that the determination of weaning is generally based on single indices, which is easily to be affected by systematic error. Additionally, the predictive performance is too low ($< 78.6\%$) that is not applicable in clinical settings. Most of the work done previously only considered indices individually by showing their powers in predicting patients who have greater probability to successfully wean from the ventilator [14-20]. The statistic analyses were done using retrospective data without conducting prospective studies. In addition, as investigated by Tobin and Jubran with meta-analysis, predictors designed using indices obtained from a single device tend to incur systematic error [21]. There are two types of errors generally encountered in an investigation: random error and systematic error. Random error can be decreased by increasing the sample size, while, if systematic error presents, an increase of sample size does not decrease it but reinforces it [23]. As manifested in previous investigations, the predictive power of successful ventilation weaning using a single index is fair [24-26]. For example, the predictive accuracy by using f/V_T is only 75-78% [25,26]. Currently, the most successful model is the one proposed by Casaseca-de-la-Higuera et al. [24] using a combination of sample entropy of 3 variables acquired from a single instrument achieving the predictive performance of only 78.6%. Hence, we suggest that adoption of multiple indices obtained from diverse instruments or modalities be expected to be able to compensate system errors incurred by indices acquired from a single instrument, which in turn elevates the predictive performance.

Computer-driven mechanical ventilators such as closed-loop knowledge-based and automated protocol-driven mechanical ventilator systems have been developed recently and used for more rapid extubation than the conventional protocol-driven ventilation [27-29]. The computer-driven system is a real-time system which acquires and interprets the patient's clinical data and gradually adjusts the level of pressure to intubated or tracheotomized patients by keeping them at a comfortable state. It was claimed to be capable of reducing the duration of mechanical ventilator and ICU stay [28,29]. The systems intend to either reduce the pressure to a minimal level to achieve spontaneous breathing while a message will be prompted on the screen to suggest a ventilator weaning [28,29] or automatically switch from mandatory to spontaneous ventilation mode if two consecutive spontaneous breaths are detected [27]. For the protocol-driven system, it will automatically switch back to the mandatory mode if continuously spontaneous breaths are no longer detected. Although computer-driven mechanical ventilators seem to be promising in facilitating ventilation weaning, before their popularity, it still needs a clinical decision support system (CDSS) to identify the earliest time when the patients can be weaned from ventilators and the patients who are likely to fail or succeed a trial of weaning based on the current settings of individual respiratory care centers (RCC).

In this study, filter and wrapper feature selection methods were used to select salient variables from 27 variables recorded in the RCC of our hospital. The filter method based on inferential statistic analyses such as t-test, Pearson chi-square test and logistic regression analysis (LRA), as well as the wrapper method based on recursive feature elimination (RFE) was adopted for feature selection. A comparison was also made to determine which feature selection method could select a better subset of features used for CDSS construction. Since support vector machine (SVM) has been recognized as a powerful computational tool for problems with nonlinearity having high dimensionalities [30-32], it was used to design a CDSS based on the selected features to assist physicians to determine if a patient can be successfully weaned from a mechanical ventilator to avoid unnecessary prolongation of period on ventilator support.

The motivations of this study are summarized as follows: (1) the successful weaning rate is too low (35-60%) if determined by physicians; (2) no agreement has been made so far to determine which physiological indices should be used for predicting successful ventilator weaning; (3) some variables are not easy to measure clinically and some are not widely monitored in ICU; (4) previous studies only focused on physiological variables, and we observed that other disease and therapeutic progression indexes should also be considered; (5) computer-driven ventilators are very expensive and not popular in general

ICUs, especially in undeveloped and developing countries; and (6) current available predictive models designed using indices acquired from a single instrument can only achieve a successful weaning rate for less than 78.6%, which still needs improvement for clinical application.

The objective of this study is to design a CDSS to achieve greater predictive performance and assist physicians in determining the right time for ICU patients to wean from mechanical ventilators successfully on daily basis without further investment of new equipment for the acquisition of additional physiological indices, thereby reducing nosocomial complications and healthcare costs. The advantages and key features of our proposed CDSS include (1) the adoption of multiple physiological indices accompanied with disease and therapeutic progression indexes; (2) a friendly and easy-to-use GUI; (3) daily-base decision support of ventilation weaning; (4) a progressive model construction by training the model using retrospective data and testing with data obtained prospectively and (5) high predictive performance.

2. **Clinical Decision Support System.** CDSS is promising in providing useful information and expert knowledge to enhance diagnostic performance and improve healthcare quality in clinical setting. Garg et al. (2005) reported that 64% of the 97 proposed CDSS applications, including 10 diagnostic systems, 21 reminder systems, 37 disease management systems, and 29 drug-dosing or prescribing systems, demonstrated improved outcomes in medical practitioner performance [33]. Apart from being applied in the diagnoses of lower back pain [34], otological disease [35], cardiovascular disease [36], and cancer using endoscopic images [37]; management and care of chronic heart failure [38] and chronic kidney failure [39]; and management of operational risk in hemodialysis [40], CDSS was also designed to care for patients who received mechanical ventilation [41-43]. A CDSS implemented as an electronic reminder was reported to be useful for nurses to increase their adherence to guidelines and to improve the positioning of patients who received mechanical ventilation [41]. Predictors including pulmonary and gastrointestine diagnoses, body mass index, and tube-feeding are important for determining head-of-bed position for patients. On the other hand, Eslami et al. reported that a significant effect was found by adopting the CDSS to improve a guideline recommending the administration of lower tidal volume for ICU patients receiving mechanical ventilation longer than 24 hours [42]. It is effective in preventing patients with acute lung injury from ventilator-associated lung injury.

3. **Material and Methods.** The experimental procedure is illustrated in Figure 1. After data collected from the patients who were managed and cared under an integrated delivery system (IDS) in the RCC strictly following the weaning protocol for consideration of ventilation weaning, variables were selected using filter and wrapper methods. The selected features are then applied for CDSS construction using SVM and neural network. The predictive performance of the CDSS was verified with cross-validation and progressive testing [31]. Finally, a program with friendly graphical user interface (GUI) had been designed to provide a tool to assist physicians in decision-making.

3.1. **Subjects and weaning protocol.** In Taiwan, the patients who need mechanical ventilator support have to be cared under the IDS mandated by the National Health Insurance Bureau (NHIB).

Patients who have been supported by mechanical ventilator for more than 14 days should be registered under the IDS and reported to the NHIB. Only the patients who are clinically stable and have been on mechanical ventilation within 21 days after starting ventilator support can be transferred to all-purpose RCCs [11]. Subjects who had been

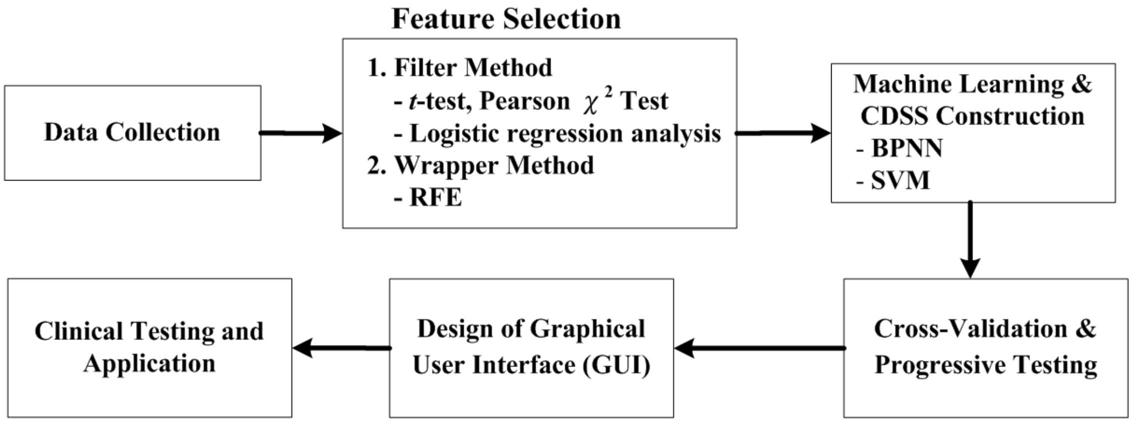

FIGURE 1. Experimental procedure

on mechanical ventilation for longer than 21 days and were clinically stable such that their primary physicians considered they were ready to undergo a weaning trial [11], were recruited at four different periods from two all-purpose respiratory care centers of a national hospital located in the central Taiwan area. Table 1 shows detailed information regarding the data collected at four different periods. The successfully weaned group consisted of patients who were able to sustain spontaneous breathing for more than 120 hours. The protocol procedure, including clinical assessment, objective test, justification of spontaneous breathing trial (SBT) and extubation of initial weaning were conducted by clinicians for ventilator weaning [43]. Those patients whose mechanical ventilators were reinstituted within 120 hours were classified as the failed weaning group. Although the data collected have spanned several years, the successful weaning rates (44%-50%) are very consistent in different periods and to the previous reports (35%-60%) [11-13].

TABLE 1. Patients recruited at three different periods

Data	Collected Period	Successful Weaning	Failed Weaning	Samples	Aggregated samples
1	Nov. 2002-Nov. 2003	83 (44.2%)	105	188	188
2	Jun. 2005-Dec. 2005	19 (44.2%)	24	43	231
3	Feb. 2008-May 2008	26 (46.4%)	30	56	287
4	Feb. 2009-Aug. 2009	30 (49%)	31	61	348
Total		158 (45.4%)	190	348	

3.2. **Support vector machine.** SVM was first developed by Vapnik and his group in former AT&T Bell Laboratories. It is a useful technique for data classification and has become an important tool for machine learning and data mining. In general, SVM has better performance when compared with other existing methods, such as neural networks and decision trees [44-46]. The goal of SVM is to separate multiple clusters with a set of unique hyperplanes having greatest margins to the boundary, consisting of support vectors, of each cluster. In contrast, each hyperplane which separates two clusters is not unique for other linear classifiers. Given a two-class linearly separable problem, the hyperplane separating two classes leaving the maximum margin from both classes is represented as [47]:

$$g(\mathbf{x}) = \mathbf{w}^T\mathbf{x} + w_0 = 0 \tag{1}$$

in which $\mathbf{w}$ indicates the weights of the input vector $\mathbf{x}$ and w_0 is a bias term of the hyperplane. The training data of two classes can be represented as $(\mathbf{x}_i, \mathbf{y}_i)$ with $x_i \in R^n$

and $y_i \in \{+1, -1\}$ for $i = 1, 2, \ldots, N$, in which sample x_i is an N-dimensional input vector and $\mathbf{y}_i$ is its corresponding label indicating the class of $\mathbf{x}_i$. By scaling the orthogonal vector $\mathbf{w}$ and bias w_0 in Equation (1) to make the values of $g(\mathbf{x})$ at the nearest points in class 1 and class 2 equal to 1 and -1, respectively, the problem of obtaining the optimal hyperplane becomes a nonlinear quadratic optimization problem, which can be formulated as:

$$\min_{\mathbf{w},w_0} \frac{\|\mathbf{w}\|^2}{2}, \text{ Subject to } y_i(\mathbf{w}^T\mathbf{x}_i + w_0) \geq 1,\ i = 1, 2, \ldots, N \tag{2}$$

The problem can be solved by considering Lagrangian duality and stated equivalently by its Wolfe dual representation form with the constraints satisfying the Karush-Kuhn-Tucker (KKT) conditions, i.e., $\partial L(\mathbf{w}, w_0, \lambda)/\partial \mathbf{w} = 0$, $\partial L(\mathbf{w}, w_0, \lambda)/\partial w_0 = 0$, $\lambda_i[y_i(\mathbf{w}^T\mathbf{x}_i + w_0) - 1] = 0$ and $\lambda_i \geq 0$ for $i = 1, \ldots, N$, as indicated in the following equation.

$$\text{Max } L(\mathbf{w}, w_0, \lambda) = \frac{\|\mathbf{w}\|^2}{2} - \sum_{i=1}^{N} \lambda_i \left[y_i(\mathbf{w}^T\mathbf{x}_i + w_0) - 1\right] \tag{3a}$$

$$\text{Subject to } \mathbf{w} = \sum_{i=1}^{N} \lambda_i y_i \mathbf{x}_i,\ \sum_{i=1}^{N} \lambda_i y_i = 0 \text{ and } \lambda_i \geq 0 \text{ for } i = 1, \ldots, N \tag{3b}$$

where $L(\mathbf{w}, w_0, \lambda)$ is a Lagrangian function and $\lambda = [\lambda_1, \lambda_2, \ldots \lambda_N]$ is the vector of Lagrangian multipliers corresponding to the constraint in Equation (2). In contrast to Equation (2), the first two constraints in Equation (3b) become equality constraints and make the problem easier to handle. By substituting the first two constraints in (3b) into (3a), the problem is formulated as:

$$\begin{aligned} &\max_{\lambda} \left(\sum_{i=1}^{N} \lambda_i - \frac{1}{2} \sum_{i,j=1}^{N} \lambda_i \lambda_j y_i y_j \mathbf{x}_i^T \mathbf{x}_j \right), \\ &\text{Subject to } \sum_{i=1}^{N} \lambda_i y_i = 0 \text{ with } \lambda_i \geq 0,\ i = 1, \ldots, N \end{aligned} \tag{4}$$

As soon as the Lagrangian multipliers have been obtained by maximizing the above equation, the optimal hyperplane can be obtained from $\mathbf{w} = \sum_{i=1}^{N} \lambda_i y_i \mathbf{x}_i$ shown in Equation (3b). And then, classification of a sample is performed based on the sign of the following equation:

$$f(\mathbf{x}) = \text{sgn}(\mathbf{w}^T\mathbf{x} + w_0) = \text{sgn}\left(\sum_{i=1}^{Ns} \lambda_i y_i \mathbf{x}_i^T \mathbf{x}_i + w_0\right) \tag{5}$$

where Ns is the number of support vectors.

For a nonlinear classification problem, the optimization problem shown in Equation (2) is changed to Equation (6) with a penalty term being added:

$$\begin{aligned} &\min_{\mathbf{w},w_0} \left(\frac{\|\mathbf{w}\|^2}{2} + C \sum_{i=1}^{N} \xi_i \right), \\ &\text{Subject to } y_i(\mathbf{w}^T \phi(\mathbf{x}_i) + w_0) \geq 1 - \xi_i \text{ and } \xi_i \geq 0,\ i = 1, 2, \ldots, N \end{aligned} \tag{6}$$

where C is a positive penalty parameter, variables ξ_i are used to weigh the cost of misclassified samples, and $\phi(\mathbf{x}_i)$ is a function applied to map the training sample x_i to a higher dimensional space. For a vector $\mathbf{x} \in \mathbf{R}^n$ in the original feature space, it is assumed that there exists a function ϕ for mapping $\mathbf{x} \in \mathbf{R}^n$ to $\phi(\mathbf{x}) \in \mathbf{R}^k$ with $k > n$. Then, the class of a sample can be determined from the following equation:

$$f(\mathbf{x}) = \text{sgn}\left[\mathbf{w}^T\phi(\mathbf{x}) + w_0\right] = \text{sgn}\left[\sum_{i=1}^{Ns} \lambda_i y_i \phi(\mathbf{x})^T \phi(\mathbf{x}_i) + w_0\right] \tag{7}$$

in which $\phi(\mathbf{x})^T\phi(\mathbf{x})_i)$ is the inner product needed for calculation and is performed by a kernel function $K(\mathbf{x}, \mathbf{z}) = \phi(\mathbf{x})^T\phi(\mathbf{z})$ which is a symmetric function satisfying the following condition:

$$\int K(\mathbf{x}, \mathbf{z})g(\mathbf{z})d\mathbf{x}d\mathbf{z} \geq 0 \text{ and } \int g(\mathbf{x})^2 d\mathbf{x} \leq \infty \tag{8}$$

Finally, the optimization problem in Equation (4) is reformulated as:

$$\begin{gathered}\underset{\lambda}{\text{Max}}\left(\sum_{i=1}^{N} \lambda_i - \frac{1}{2}\sum_{i,j=1}^{N} \lambda_i\lambda_j y_i y_j K(\mathbf{x}_i^T\mathbf{x}_j)\right), \\ \text{Subject to } \sum_{i=1}^{N} \lambda_i y_i = 0 \text{ with } 0 \leq \lambda_i \leq C\end{gathered} \tag{9}$$

For a nonlinear classifier, various kernels including polynomials, radial basis functions, and hyperbolic tangents can be used for mapping the original sample space into a new Euclidian space with Mercer's conditions satisfied. The linear classifier can then be designed for classification. Among them, radial basis function, as shown in the following equation, is the most widely used function and is adopted in this study for feature mapping.

$$K(\mathbf{x}, \mathbf{z}) = \exp(-\gamma \left\|\mathbf{x} - \mathbf{z}\right\|^2) \tag{10}$$

Recently, design of CDSSs using SVM has grown rapidly in the diagnosis of cardiovascular disease [36], hypertension [48], and breast cancer [49-51], and in the discrimination of cervical lymph nodes as malignant or benign during ultrasonography [52]. In this study, SVM was applied to construct a CDSS for the prediction of successful ventilator weaning. The effectiveness is compared with the model built with an artificial neural network.

Since the ranges of individual variables have great variations, a normalization scheme was applied to adjust the data to lie within a range between 0 and 1 for all variables. For cross validation, all the sample data were randomly divided into n clusters (folds), in which $n - 1$ folds were used for training while the remaining one for testing the accuracy of the model. In this study 6-fold cross-validation was adopted. In this case, data were divided into 6 folds, in which 5 folds were used as the training set and the remaining one as the testing set. The procedure was repeated 6 times and then the average sensitivity, specificity, and accuracy were calculated for a cycle of cross validation. In order to eliminate the bias produced in sample groupings for only 1 cycle of cross validation, 10 repeated cross-validations were done to obtain the mean and standard deviation of the average accuracy, sensitivity and specificity of individual cycles.

3.3. **Feature selection.** Feature selection takes the advantage of reducing the number of features and the size of storage requirements, decreasing training and computational time, facilitating data visualization and understanding, and improving predictive performance [53,54]. The algorithms of feature selection can often be classified into 3 approaches including filter, wrapper, and embedded methods [53]. The filter method is a preprocessing procedure which selects a subset of features based on statistic measures independent of the designed classifiers. In contrast, the wrapper method assesses individual subsets of features in a recursive way by considering their predictive efficiency to a given classifier. It is more computational intensive than the filter method, but is believed to able to provide more efficient outcome. The subset with the smallest number of features achieving the highest predictive accuracy is used for classifier construction. Recently, genetic algorithm, an alternative wrapper method, was also proposed as a useful method for feature selection [55,56], and sometimes, this strategy is also used for the adjustments of cost value and kernel parameter of SVM together with the selection of features when designing a classifier [57]. For example, it was applied to construct predictive models for the diagnoses of breast cancers [50,51] and hypertension [48]. On the other hand, the embedded method selects features during the process of model construction by considering the cost function of a model [58], for example the function shown in Equation (6) for SVM model.

3.3.1. *Filter method based on logistic regression analysis.* The filter approach used for feature selection in this study is based on LRA. It is a type of nonlinear regressions which has been used to delineate the relationship between several independent variables, discrete or continuous, and a dependent discrete variable, dichotomous or multiple. For binary LRA, the dependent variable is dichotomous, while for multiple LRA, it is multiple. In contrast, the dependent variable of a multiple regression analysis is continuous. The dependent variable (y) is a linear combination of dependent variables (x_i) for a multiple regression, as shown in the following equation:

$$y = a + \sum_{i=1}^{n} b_i x_i + \varepsilon \tag{11}$$

in which a is the intercept of Y axis, b_i indicates the regression coefficient, and ε is the prediction error. Therefore, a model constructed using multiple regression analysis can be represented as:

$$g(\mathbf{x}) = a + \sum_{i=1}^{n} b_i x_i \tag{12}$$

Hence, the prediction error $\varepsilon = y - g(\mathbf{x})$ indicates the difference between a measured value and the predicted value. Since the dependent variable of a binary LRA is dichotomous, i.e., 1 or 0, it's modeling is based on the probability associated with the values of dependent variable, as formulated as natural logarithm of odd ratio in favor of $y = 1$ in the following equation.

$$\ln \frac{P(y = 1|x_1, x_2, \ldots, x_n)}{P(y = 0|x_1, x_2, \ldots, x_n)} = a + \sum_{i=1}^{n} b_i x_i \tag{13}$$

The above (Logit) transformation of the dependent variable converts a non-linear relationship between independent and dependent variables into a linear one. The SPSS 12.0 statistical software package was adopted to perform a statistical analysis of the acquired data. Descriptive statistics were first used to overview the characteristics of the dataset with mean and standard deviation calculated for each continuous variable followed by inferential statistics. Frequency and percentage of each sub-type of a categorical variable were also calculated for further analysis. Inference statistics such as t-test was used to test significance of the continuous variables while a Pearson chi-square test was applied to test the dichotomous variables. The variables which are significantly different ($p < 0.05$) between successful and failed weaning groups were further studied using LRA. In the beginning, all of the 27 variables were analyzed using t-test and Pearson chi-square test for selecting salient continuous and discrete variables, respectively, which was then followed by LRA to further select significant variables for CDSS training and testing using neural network and support vector machine. The 27 variables of the collected data are presented in Table 2. It depicts the effects of demography, physiology and disease, and care and treatment factors on a ventilator weaning prediction. Significant variables were selected from the collected data for constructing the CDSS. The performances of two machine learning methods, i.e., SVM and neural network, were compared.

Table 2. Statistic analyses of 27 recorded variables for feature selection (N = 287)

Variables	Ventilator Weaning		
	Successful ($n = 128$)	Failed ($n = 159$)	Significance (p-value)
Demographic Data			
Gender (male/female)	76/52	93/66	0.88
Age	72.10 ± 14.17	76.72 ± 13.27	0.005^*
Physiology and Disease Factors			
APACHE II score at hospitalization	17.31 ± 4.93	18.79 ± 5.88	0.024^*
Coma Scale at hospitalization	9.69 ± 3.42	9.33 ± 3.93	0.422
Albumin (mg/dl)	2.80 ± 0.48	3.08 ± 3.7	0.403
Blood urea nitrogen (BUN) (mg/dl)	26.22 ± 18.23	39.10 ± 30.22	$< 0.001^{**}$
Creatinine (mg/dl)	1.29 ± 0.99	4.36 ± 22.34	0.121
Hemoglobin (g/dl)	10.90 ± 1.63	10.51 ± 5.99	0.479
Pulmonary disease	74 (57.8%)	86 (54.1%)	0.528
Cardiac disease	22 (17.2%)	31 (19.5%)	0.616
Historical respiratory disease	28 (21.9%)	57 (35.8%)	$0.01^\dagger$
Brain vessel disease	15 (11.7%)	11 (6.9%)	0.159
Other causes related to int. medicine	66 (51.6%)	107 (67.3%)	$0.007^\dagger$
Acute respiratory distress syndrome	3 (2.3%)	0 (0%)	0.052
Multiple-organ failure	0 (0%)	7 (4.4%)	$0.016^\dagger$
Trauma	0 (0%)	3 (1.9%)	0.118
Brain Surgery	30 (23.4%)	17 (10.7%)	$0.004^\dagger$
Other kinds of surgeries	7 (5.5%)	19 (11.9%)	0.249
Care and Treatment Factors			
Tracheotomy	61 (47.7%)	62 (37.7%)	0.14
Coma scale at weaning	9.37 ± 2.93	7.41 ± 2.96	$< 0.001^{**}$
RSBI at weaning	91.52 ± 43.28	161.05 ± 79.76	$< 0.001^{**}$
Length of ICU admission (day)	16.02 ± 7.08	17.97 ± 6.85	0.019^*
Days using ventilator	32.67 ± 12.45	41.11 ± 17.31	$< 0.001^{**}$
Ventilator associated pneumonia	16 (12.5%)	61 (38.4%)	$< 0.001^\ddagger$
Blood infection	0 (0%)	6 (3.4%)	$0.026^\dagger$
Urinary tract infection	14 (10.9%)	41 (25.8%)	$< 0.001^\ddagger$
Nosocomial infection	6 (4.7%)	6 (3.4%)	0.701

t-test: $p \leqq 0.55^*$, $p \leqq 0.001^{**}$; Pearson χ^2 test: $p \leqq 0.55^\dagger$, $p \leqq 0.001^\ddagger$

3.3.2. *Wrapper method based on recursive feature elimination.* The wrapper method assesses individual subsets of features in a recursive way by considering their predictive efficiency to a given classifier. For a vector space with n features, recursive feature elimination (RFE) algorithm removes unimportant features based on backward sequential selection by iteratively deleting one feature at a time, resulting in a sub-optimal combination of r ($r < n$) features with best predictive performance [53]. For SVM-RFE, it starts with all features by deleting a feature repeatedly until r features are left, which leads to a largest margin separating two classes. Weight magnitude which is inversely proportional to the margin is generally used as the ranking criterion in determining the importance of individual features. The eliminated feature p is the one which minimizes the variation of weight:

$$\|\mathbf{w}_{-p}\|^2 = \sum_{i,j=0}^{N} \lambda_i \lambda_j y_i y_j K(\mathbf{x}_i^T \mathbf{x}_j) \tag{14}$$

In addition to weight or margin, other measures such as generalization error [58], gradient of weight [59] and Fischer's ratio [60] were also proposed for feature ranking [58]. In this study, mean cross validation accuracy was used as a measure of feature ranking for determining the eliminated feature in each iteration.

3.4. **Progressive CDSS designs.** Since the weaning data are not easy to collect, it is not possible to construct a CDSS with high performance without using a lot of samples. Hence, in this study, we proposed a strategy, namely progressive CDSS construction, for gradually improving CDSS performance. First of all, the data collected at the first period was used to construct the CDSS with the scheme of cross validation used to verify effectiveness of the system. Secondly, the data collected during the second period were applied to test the performance of the model. Thirdly, the data collected from the second period were pooled to the preciously collected data and the training and testing procedures were repeated. Fourthly, the data collected in the third period were again used to test the revised CDSS. The above procedure will be repeated until the system is stabilized. As demonstrated in the next section, the results show that the performance of the CDSS has gradually improved by using more data. In future clinical application, patient data collected within a certain period of time containing enough samples will be pooled to the existing dataset for CDSS reconstruction and testing. The procedure will be repeated until the CDSS has achieved optimal performance.

3.5. **Design of CDSS.** A computer-assisted decision support system was designed to provide physicians with a useful tool for making weaning decisions. The graphic user interface (GUI) of the prototypic CDSS designed with SVM using 11 features selected based on RFE is shown in Figure 2. As shown in this figure, the values of salient variables (upper-left corner) can be input to the system for weaning prediction. Other accompanied variables (right column) can also be input and stored for later analysis. If the predicted successful probability is higher than a threshold (0.5), the system predicts that the patient can be weaned successfully.

4. **Results.**

4.1. **Feature selection.** Table 2 shows the results of descriptive statistics and inference statistics of 27 recorded variables for the dataset containing 287 samples collected in the first three periods. As depicted in this table, 7 continuous variables and 7 discrete variables are significantly different ($p < 0.05$) between successful and failed weaning groups. After pooling the 14 variables together, a filter method based on LRA was used for further analysis and feature selection. As shown in Table 3, it was found that only 7 variables, including blood urea nitrogen (BUN), brain surgery, coma scale when weaning, rapid shallow breathing index (RSBI) when weaning, days using ventilator, ventilator associated pneumonia, and urinary tract infection, were significant ($p < 0.05$) and selected for CDSS construction. Other aggregated datasets, which consist of 188, 231, and 348 samples, also demonstrated similar characteristics such that only 7 variables reached significance ($p < 0.05$) after LRA.

The accuracy against the number of selected features based on SVM-RFE method is shown in Figure 3. As indicated in this figure, using 11 features for the design of a CDSS

Figure 2. Graphic user interface of the designed CDSS

Table 3. Significant variables after logistic regression analysis

Variables	B	S.E.	Wald	*P*-value
Blood urine nitrogen	0.016	0.007	4.856	0.028*
Brain surgery	−1.191	0.455	6.861	0.00*
Coma scale at weaning	−0.313	0.063	24.319	$<0.001^{**}$
RSBI at weaning	0.017	0.003	28.827	$<0.001^{**}$
Days using ventilator	0.026	0.011	5.855	0.016*
Ventilator associated pneumonia	1.172	0.378	9.601	0.002*
Urinary tract infection	1.429	0.438	10.640	0.001*
Constant	−1.004	0.769	1.704	0.192

$^{*}p \leqq 0.55$, $^{**}p \leqq 0.001$

model achieves maximum accuracy. To compare the features selected using LRA (Table 3) and SVM-RFE (Figure 2), it was found that 5 common features, i.e., coma scale at weaning, RSBI, days using ventilator, ventilator associated pneumonia and urinary tract infection, were selected by two methods, while brain surgery and BUN were selected only by LRA, but coma scale at hospitalization, creatinine, pulmonary disease, brain vessel disease, tracheotomy and other causes related to internal medicine were selected by SVM-RFE alone.

4.2. **Weaning prediction.** In the first experiment, we tested SVM models using different combinations of parameters, C and γ, with a grid size of 0.1 to select the optimal parameters for constructing the CDSS with greatest predictive accuracy. As shown in Table 4, the optimal SVM parameters were different for different datasets containing data collected at different aggregated number of periods, i.e., 1, 2, 3 and 4 periods, respectively. In addition, features selected using different methods of feature selection also

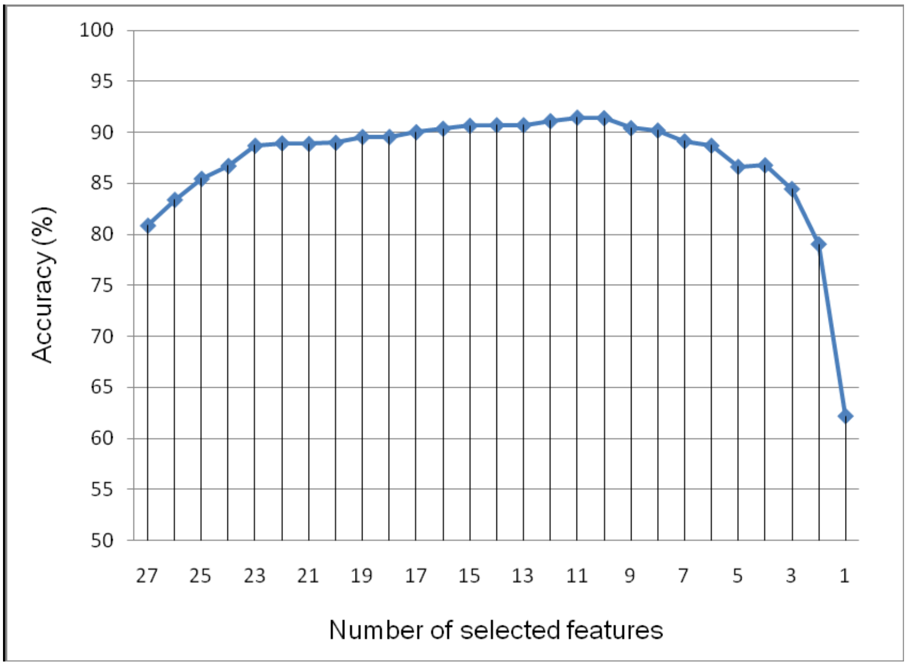

Figure 3. Maximum accuracy against number of selected feature using SVM-RFE method

affect the optimal parameters because of different number or combination of selected features. Performance evaluation was done using 6-fold cross-validation and the experiments were repeated 10 times for each case. The mean accuracy, sensitivity, and specificity achieve larger values for the cases with more data samples. It is also observed that the predictive performance for the CDSS model constructed using features selected based on wrapper method (11 features) is better than filter method (7 features).

Table 4. Optimal SVM parameters of different datasets containing different number of samples for model construction using different combination of features selected using filter methods (7 features) and wrapper methods (11 features), respectively. Notice that 6-fold cross-validation was used to test performance using grid search for 10 repetitions. The accuracy, sensitivity and specificity for wrapper method are better than filter method.

Sample Size	**Feature Selection**	**Accuracy (SD) (%)**	**Sensitivity (SD) (%)**	**Specificity (SD) (%)**	$\log_2 \mathbf{C}$	$\log_2 \gamma$
348	Filter	88.33 (0.84)	90.32 (1.46)	85.86 (1.18)	32	16
	Wrapper	92.73 (0.79)	95.81 (0.94)	88.97 (1.96)	6.2	3.1
287	Filter	85.19 (1.55)	92.17 (0.87)	73.97 (3.48)	4	64
	Wrapper	90.56 (1.37)	95.14 (2.05)	85.00 (2.34)	5.9	3
231	Filter	78.73 (1.57)	91.08 (1.03)	63.77 (3.28)	0.0625	64
	Wrapper	85.27 (1.57)	92.34 (2.41)	76.35 (2.63)	4.8	3
188	Filter	77.16 (1.16)	86.55 (1.79)	64.91 (1.72)	0.5	8
	Wrapper	79.88 (1.34)	91.42 (1.32)	76.35 (4.13)	6	3.2

In the second experiment, the CDSS was constructed using the data collected at the first q periods, $1 \leqq q \leqq 3$, and then the data of the $(q+1)$th period were applied for testing the system. For $q = 1$, the data collected at the first period were used for training the CDSS and the data of the 2nd period applied for testing the CDSS model. In this case, prediction accuracy of 72.10% and 81.43% was obtained for features selected with filter and wrapper methods, respectively. As shown in Table 5, the procedure was repeated for 3 times with predictive accuracies of 72.10%, 89.36% and 90.15%, respectively, for models constructed using 7 features and 81.43%, 89.36% and 91.25%, respectively, using 11 features. As indicated in this table, the CDSS has been improved progressively by using more samples for training. The predictive rate raised more than 8% when the number of training samples increased from 188 to 231, while it was less than 2% improvement when the number of training samples increased from 231 to 287.

A comparison of predictive rates for CDSS models constructed using two different models, i.e., SVM and back-propagation neural network (BPNN), was also demonstrated in Table 5. As indicated in this table, SVM model achieves higher predictive rates than BPNN for all cases.

Table 5. Comparisons of progressive models with the data collected at previous periods used for training and the data at the following period as testing

Training Samples	**Testing Samples**	**Feature Selection**	**Accuracy (%)**		**Sensitivity (%)**		**Specificity (%)**	
			SVM	**BPNN**	**SVM**	**BPNN**	**SVM**	**BPNN**
188	43	Filter	72.10	70.00	79.17	74.17	63.16	64.21
		Wrapper	81.43	75.53	86.23	78.83	74.78	70.00
231	56	Filter	89.36	83.75	90.00	93.33	87.67	72.69
		Wrapper	89.36	83.39	91.78	93.67	86.75	71.15
287	61	Filter	90.15	83.93	91.00	94.84	89.21	73.33
		Wrapper	91.25	88.69	92.56	93.55	87.89	82.33

5. **Discussion.** To minimize the duration of mechanical ventilation, the clinician should define and treat the underlying causes of respiratory insufficiency and discontinue machine support at the earliest possible time. MacIntyre et al. (2001) suggested that four criteria should be assessed before discontinuing ventilation for patients with acute respiratory failure: (1) the causes inducing respiratory failure have been reversed; (2) adequate oxygenation and pH value of blood; (3) stable homodynamic without active myocardial ischemia and hypotension and (4) the ability to initiate inspiration. In this study, the physicians were asked to follow the above criteria [5]. For patients who met the above criteria, the physicians would soon consider the possibility for the patients to have trials of ventilation weaning and extubation.

On the other hand, The American College of Chest Physicians, the Society of Critical Care Medicine and the American Association for Respiratory Care also created five evidence-based guidelines for ventilator weaning based on the following principles. First, frequent assessment is required to determine whether ventilator support and the artificial airway are still needed. Second, patients who continue to require support should be continually re-evaluated to assure that all factors contributing to ventilator dependence are addressed. Third, with patients who continue to require support, the support strategy should maximize patient comfort and provide muscle unloading by fitting the physical needs for individual patients and tuning the operational modes of ventilators to enable them not to fight the usage of ventilators and to make them feel as comfortable as possible. Fourth, patients who require prolonged ventilator support beyond the intensive care unit should go to specialized facilities that can provide more gradual support reduction strategies. Finally, ventilator-discontinuation and weaning protocol can be effectively carried out by non-physician clinicians. The designed CDSS is efficient in realizing the first two guidelines under the supervision of physicians. As soon as the mechanical ventilator has been successfully weaned, general healthcare providers will take over the patients.

5.1. **Predictive variables.** A number of physiologic indices have been described to predict the outcome of attempts at discontinuing ventilator support. Previous investigations showed that several physiological indexes, such as rapid shallow breathing index [14], maximal inspiration pressure (PImax) [15,16], vital capacity (VC) [16], minute ventilation (VE) [15,17] and pH and pCO2 values of stomach mucosa [18], were useful for successfully predicting ventilation weaning. It was also shown that several variables, such as arterial blood gas levels, fraction of inspired oxygen, alveolar-arterial oxygen pressure difference (A-a gradient), blood urine nitrogen (BUN) level, serum creatinine level and serum albumin level, were correlated to successful weaning [19,20]. In addition to BUN level and albumin level [12], race and reason for ventilator dependency were also found to be major predictors. However, some of the above indices are difficult to measure and cannot be applied in daily practice.

Chen et al. (2005) found that patients with lower APACHE II scores had higher incidences of successful weaning from the ventilator in Respiratory Care Center (RCC), which was also observed in this study (Table 2, $p < 0.05$) [61]. In addition, it was reported that long-term survival was inversely associated with age and length of stay in ICU or RCC [20]. This finding is consistent with our statistical outcome that patients with larger age ($p < 0.01$) and longer ICU stay ($p < 0.05$) were more difficult to wean from mechanical ventilation. However, these three variables were not selected for CDSS construction. The main reason might be that they are not compatible with other more important selected variables. Furthermore, as shown in Table 2, according to our dataset historical respiratory disease, multiple organ failure, and blood infection are indeed statistically significant variables ($p < 0.05$) for discriminating successful and failed weaning patients if considered individually. Unfortunately, they have been filtered out by both LRA and SVM-RFE as well because they might not be independent to other salient variables. For example, APACH II is calculated based on several variables including age, disease and biochemical data.

In this study, the predictive performance of the CDSS constructed with SVM using the 11 aforementioned variables is considerably better than that of tradition indices used in previous investigations, such as PImax [15,16], vital capacity (VC) [16], and minute ventilation (VE) [15,17]; arterial blood gas levels, fraction of inspired oxygen, alveolar-arterial oxygen pressure difference (A-a gradient), blood urine nitrogen (BUN) level, serum creatinine level, and serum albumin level [19,20] and age and length of stay in ICU and RCC [20]. The model proposed here outperforms previous predictors with accuracies of 75-78% using f/V_T as the predictive index [25,26] as well as a recently reported predictor with an accuracy of 78.6% using a combination of sample entropy of three variables including inspiratory tidal volume (VTI) and expiratory tidal volume (VTE), and respiration rate (RR) [24].

Among the variables, BUN [19,20], RSBI [6,14] and days using ventilator [20] were also adopted in this investigation. Specifically, Meade et al. found that RSBI is the most frequently studied and one of the most powerful indexes in successful weaning [6]. From our understanding, variables including brain vessel disease, coma scales at weaning, ventilator associated pneumonia, trachectomy, and urinary tract infection used in this study have never been reported elsewhere as indicators of weaning prediction. Weaning failure is usually multifactor in nature. Although a number of physiologic indexes have been described to predict the outcome of attempts at discontinuing ventilator support, indexes that assess a single physiologic function are frequently inaccurate predicators.

Unfortunately, previous studies only focused on physiological variables. We suggest that other disease and therapeutic progression indexes should also be considered.

5.2. **A comparison between SVM and BPNN.** Neural network and decision tree have been widely applied in designing decision systems for clinical applications. Some of the studies support that neural network is better than decision tree [62-64] while others have opposite outcomes [65]. Recently, application of SVM in medicine has grown rapidly. For example, it has been applied in prediction of RNA-binding sites in proteins [66], discrimination of malignant and benign cervical lymph nodes [52], disease diagnosis using tongue images [67], and diagnoses of cardiovascular disease [36] and breast cancer [49]. Wu et al. (2008) applied artificial neural network and support vector machine to diagnose the learning disabilities (LD) problem for students [68]. Although their results showed that neural network performs better than SVM, other investigations reported that SVM in general has better performance when compared with neural networks and decision trees [44-46]. In this study, we compared the models constructed using BPNN and SVM under various sample sizes aggregated from various periods, the results show that CDSS constructed using SVM outperforms the model constructed using BPNN in weaning prediction, which is consistent to some reports [44,45] but contradicts to the result obtained by [68]. We suspect that different characteristics of variables and sample sizes might be the reason causing such a differentiation.

The predictive accuracy of model constructed using LRA alone without applying SVM was also evaluated with only 76% of predictive accuracy being achieved for the case of 287 samples, which is significantly lower than the SVM models constructed using either 7 (85.19%) or 11 variables (90.56%). There are two ways, transform either independent or dependent variables, to change nonlinear relationship between independent and dependent variables into a linear one. One possible reason for low predictive accuracy of LRA model might be that it transformed the dependent variable using a nonlinear logarithmic function and constructed in the same dimensional space, while the SVM models transform the input variables to a space with higher dimensions using a nonlinear kernel before being classified linearly in the high-dimensional space.

5.3. **Clinical application.** A Clinical Decision Support System (CDSS) has been designed and applied in clinical setting of a national hospital situated in central Taiwan. Weaning tests were conducted daily by measuring physiological variables of patients and then, accompanied with disease factors and care and treatment factors, input to the CDSS for determining if a patient can be weaned. A condition imposed is that for patients whom the CDSS predicts to have great probability of successful ventilator weaning, the protocol of initial weaning including clinical assessment, objective test, justification of an SBT and extubation, as detailed below, will be conducted by clinicians [43].

1. Clinical assessment: the patient's clinical situations, including adequate cough, absence of excessive tracheobronchial secretion, and resolution of disease acute phase for which the patient was intubated, are assessed to determine if he/she can be considered to wean.
2. Objective test: the patient is tested to determine if he/she meets the following criteria: clinical stability, adequate oxygenation, adequate pulmonary function, and adequate mentation. Patients who meet the criteria could be considered as being ready to wean from ventilation.
3. Justification of an SBT: an SBT should be considered as soon as possible once the patient meets the aforementioned criteria. Criteria for passing SBT include respiratory pattern, adequate gas exchange, hemodynamic stability and subject comfort.

4. Extubation: patients who successfully pass the SBT should be extubated if neurological status, excessive secretions and airway obstruction are not critical issues.

If a patient fails in the initial weaning trial, he/she will be kept staying in the respiratory care center (RCC) for continuous monitoring and therapy until the maximum admission days of 63 days has terminated. Patients who have been admitted in RCC for more than 63 days of ventilator usage without successful ventilation weaning trial will be transferred to the respiratory care ward (RCW) for afterward chronic care according to the national health insurance regulation of Taiwan.

The system has been applied in clinical setting from Feb. 2010 to Jan. 2010 and demonstrated to be efficient in reducing the period of ventilator use for more than 1 day in average with a saving of NT$9000 (around US$300) per patient, as well as in achieving a predictive accuracy of 90.1%.

6. **Conclusion.** Most of the work done previously only considered indices individually by showing their powers in predicting patients who have greater probability to successfully wean from ventilator. The statistic analyses were done using retrospective data without conducting prospective study in previous investigation. The novelty of this study is that multiple indices, including physiological indices obtained from various instruments daily accompanied with disease as well as care and treatment factors, were adopted for designing the CDSS. It has been demonstrated that multiple indices obtained from various instruments or modalities are able to compensate systematic errors incurred by indices acquired from a single instrument, which in turn is effective in elevating predictive performance. Additionally, progressive modeling was proposed to construct models using retrospective data and tested with data obtained prospectively. This contrasts with previous investigations that only retrospective data were used for statistic analyses to find useful indices.

In this study, in contrast to extubation failure by some investigations, weaning failure was adopted as the outcome end point [21]. As shown in Table 5, the significance of the results presented is that the designed CDSS achieves a predictive accuracy of 91.25%, which outperforms previous studies using f/V_T as the predictive index achieving accuracies ranging from 75-78% [25,26] and a model proposed recently using a combination of sample entropy of three variables with an accuracy of 78.6% [24]. Our model was shown to be able to achieve better predictive performance and reduce healthcare cost in clinical setting.

In order to reduce the systematic error induced by the CDSS designed using indices acquired from a single device, multiple indices obtained from various instruments were adopted for designing the CDSS using SVM. To further improve the predictive performance of the CDSS, feature-selection technique was applied to select salient feature. The wrapper method (SVM-RFE) was demonstrated to be capable of obtaining better combination of features, 11 features in this case, with better predictive performance (91.46%) than the filter (LRA) method. Furthermore, two validation methods, cross-validation and progressive testing, were used to test efficacy of the constructed system. A program with GUI was design to assist clinical doctors in decision-making for determining which patients have great probability to be weaned successfully. The predictive rate of the CDSS constructed using SVM with 11 selected salient variables achieves as high as 92.73% for cross-validation and 91.25% for progressive testing, which outperforms the models using f/V_T (75-78%) and a model (78.6%) proposed recently using a combination of sample entropy of three variables, i.e., inspiratory tidal volume (VTI), expiratory tidal volume (VTE) and respiration rate (RR) [24].

The key features and advantages of our proposed CDSS include (1) adoption of diverse physiological indices acquired from multiple instruments accompanied with disease factors as well as therapeutic progression indices; (2) friendly and easy-to-use GUI; (3) daily-base decision support of ventilation weaning; (4) progressive model construction by training the model using retrospective data and testing with data obtained prospectively and (5) high predictive performance. A preliminary result of this investigation was reported in [69].

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