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SYSTEMS-LEVEL QUALITY IMPROVEMENT

An ensemble learning method for asthma control level detection with leveraging medical knowledge-based classifier and supervised learning

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Abstract

Approximately 300 million people are afflicted with asthma around the world, with the estimated death rate of 250,000 cases, indicating the significance of this disease. If not treated, it can turn into a serious public health problem. The best method to treat asthma is to control it. Physicians recommend continuous monitoring on asthma symptoms and offering treatment preventive plans based on the patient's control level. Therefore, successful detection of the disease control level plays a critical role in presenting treatment plans. In view of this objective, we collected the data of 96 asthma patients within a 9-month period from a specialized hospital for pulmonary diseases in Tehran. A new ensemble learning algorithm with combining physicians' knowledge in the form of a rule-based classifier and supervised learning algorithms is proposed to detect asthma control level in a multivariate dataset with multiclass response variable. The model outcome resulting from the balancing operations and feature selection on data yielded the accuracy of 91.66%. Our proposed model combines medical knowledge with machine learning algorithms to classify asthma control level more accurately. This model can be applied in electronic self-care systems to support the real-time decision and personalized warnings on possible deterioration of asthma control level. Such tools can centralize asthma treatment from the current reactive care models into a preventive approach in which the physician's therapeutic actions would be based on control level.

Keywords Asthma control · Ensemble learning · Medical knowledge · Rule-based · Self-care

Introduction

Asthma is a multifactorial, heterogeneous and periodical disease created or exacerbated among the genetically apt people under environmental exposures [1]. The nature of asthma and its various exacerbating stimuli have made the management of this disease a challenging issue [2].

Older guidelines classify asthma based on its severity and then underpin the treatment process only upon the same factor. Many physicians, however, argue that such approach in the phase of guidelines implementation has various weaknesses [3]. The most important issue is to answer the question that how one can classify a disease with highly variable and fluctuating nature into such fixed indices and provide the treatment only based on its severity [4]. For this reason, the National Asthma Education and Prevention Program (NAEPP-EPR3) in its Expert Panel Report suggested that physicians start the treatment based on the asthma severity, and then set up the treatment plan based on the asthma control level [5]. In other words, NAEPP-EPR3 recommends that the

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changes in treatment plan should be based on the answer to another simple question: "Is asthma under control?" [6].

To achieve desired asthma control level, before everything, evaluation of control level by the physician for making any changes in the treatment plan is required [7, 8]. NAEPP-EPR3 divides asthma control into three levels, and suggests the physicians to adopt a step-by-step pharmaceutical treatment approach based on the level in which the patient's condition is permanently monitored [5].

The important point is that in most cases, asthma control level is not properly estimated; this issue is more frightening when it is estimated more desirably than the reality [4]. Accurate detection of asthma control level can lead to pre-awareness about the deterioration of the disease control, and when the patient is on an inappropriate control status, the required warnings will be submitted to him/her to take urgent measures [4]. As a result, since the importance of asthma control has recently become an integral part of most of therapeutic interventions in this field, we intend to detect it with suitable tools in this study.

Review of literature

Review of the related literature shows that what differentiates the asthma control studies from each other relies on answering the following questions: "What is the objective of examining asthma control?", "What kind of stimuli affects asthma control?" and "What are the analytical tools with what degree of accuracy applied for this purpose?" Table 1 presents the summary of previous studies on asthma control assessment area.

Reviewing the studies reveals that scholars have focused on three main objectives:

- Predicting asthma attacks as an event resulting from the most undesired control level [2, 9–17]
- Predicting the deterioration of asthma control level [4, 17]
- Predicting asthma control level [18, 19]

The first two objectives focus on predicting undesirable events much late, while they can be prevented much earlier when the disease is at an uncontrolled level. Only two recently published papers have focused on predicting the level of control. For this purpose, the present study classifies asthma control level into three classes of well-controlled, not well-controlled, and very poorly-controlled, which have not been taken seriously into account in previous studies.

In terms of stimuli, the related articles (Table 1) can be differentiated based on the stimuli effective on asthma control. These stimuli can be categorized into seven groups as below:

1. Group of stimuli based on environmental data
2. Group of stimuli based on the patient's demographic information
3. Group of stimuli based on the patient's medical history and clinical variables
4. Group of stimuli based on the lung function
5. Group of stimuli based on genetic factors
6. Group of stimuli based on biomarkers
7. Group of stimuli based on symptoms derived from the questionnaires of asthma control

Each of the above groups has different sub-stimuli, all or a part of which has been already studied in the literature. In this paper, the considered stimuli include the patient's demographic features, clinical variables and the patient's medical history, environmental data, the lung function, and group of stimuli based on the Asthma Control Test (ACT). In this study, we could not access two groups of stimuli: genetic factors and biomarkers.

Regarding the analysis of data, research evidence shows that previous studies have been limited to using traditional statistical methods, data mining and machine learning techniques (Table 1) such as regression, decision tree and so on [13, 20] to classify the level of control while their results indicate that adopting this methods alone is not sufficient. Compared to traditional methods of classification, new machine learning techniques such as ensemble learning provide better performance in many cases [21] and the their potential has not yet been addressed in improving the classification of asthma control level. On the other hand, there is a rich literature on incorporating experts' knowledge as informative priors with machine learning techniques to achieve the maximum classification accuracy [21]. Physicians' knowledge can be transformed into if-then rules in a rule engine and then used in the form of a rule-based classifier [22–24]. Concerning the classifier, it is important to identify that physicians consider what characteristics and rules according to their knowledge and practice to assess level of asthma control.

With this in mind, we propose an ensemble learning algorithm to derived from the combination of physicians' knowledge as well as supervised learning algorithms to improve the results of asthma control level detection. In fact, to build a powerful classification model, it is necessary to select an appropriate integration of models and the stimuli affecting asthma control.

Ensemble learning

Ensemble methods are learning techniques that combine a number of base learners in a parallel or sequential style and then classify new data points through weighted voting of their predictions to obtain better predictive performance compared to individual base learners that make them up [25]. In present study, we use an ensemble averaging approach, that is one of the two major types of static committee machines. In ensemble averaging, outputs of a set of different predictors with low bias and high variance, are linearly combined to produce an overall output [26].

Table 1 Summary of previous studies conducted on asthma control area

Author (year)	Research objective	Population	Variables group							Method	Performance evaluation
			Medical history	Growth characteristics	Symptoms	Lung function	Biomarker	Genetic	Environmental factors		F-Score (%)
Arvanitis et al. (2018)	Predicting asthma control	48 patients, A total of 1100 records collected based on a daily assessment of asthma control.			*					Gaussian mixture model	75.12
Kocsis et al. (2017)	Predicting asthma control	39 patients, A total of 698 records collected based on a daily assessment of asthma control.			*	*				Support vector machine Random forest AdaBoost	
Honkoop et al. (2017)	Predicting asthma control deterioration & exacerbation	150 patients, A total of 6300 records collected based on daily entries of measurements.		*		*	*		*	Bayesian network A spatial–temporal model	
Toti et al. (2016)	Predicting asthma attack	Data related to 20,959 pediatric ED visits.							*	Association rule	
Luo et al. (2015)	Predicting asthma control deterioration	210 patients, A total of 2912 records collected based on weekly assessments of asthma control.	*	*	*				*	Multi boost with decision stumps Support vector machine Deep learning Naive Bayes K-nearest neighbor Random forest	49.38 48.76 48.96 50.50 44.10 40.64
Vliet et al. (2015)	Predicting asthma attack	96 asthmatic children in one-year prospective observational study, with clinical visits every 2 months.		*	*	*	*			K-nearest neighbor	45.16
Kupczyk et al. (2015)	Predicting asthma attack	169 patients, data collected over a 1-year period using electronic diaries.	*	*	*	*	*			Multivariate logistic regression	
Bateman et al. (2014)	Predicting asthma attack	7446 patients.	*	*	*	*				Logistic regression	
Finkelstein et al. (2013)	Predicting asthma attack	26 patients, A total of 7001 records collected based on			*					Support vector machine Naive Bayes	

Table 1 (continued)

		self-reports during home tele monitor-ing.								
Farion et al. (2013)	Predicting Asthma attack	240 patients.	*	*	*				Naive Bayes Decision tree Ensemble of decision tree Support vector machine Instance-based model	76.77
Wu et al. (2012)	Predicting Asthma attack	1041 patients.		*		*			Markov model	
Lee et al. (2011)	Predicting Asthma attack	33 asthmatic children.		*	*			*	Pattern based decision tree Pattern based association rule	
Xu et al. (2011)	Predicting Asthma attack	417 patients.	*	*		*	*	*	Random forest	72.73

Let X, Y, H, and T denote the instance space, the set of class labels, the set of base learners, and the number of base learners, respectively. A training dataset D= {(x_1,y_1), …, (x_m,y_m)} is given, where $x_i \in X$ and $y_i \in Y$ (i = 1, …, m). Also, base learners are denoted by $h_i \in H$ (i = 1, …, t). The learner is a hypothesis about the true function f. Given new data points x, f predicts the corresponding y values. The implementation steps of the ensemble method used in this study include the following steps:

1. Training each base learner separately, each with their own initial value (each learner is tuned with K-fold cross-validation and optimal initial parameters are set).
2. Given an unlabeled instance x: predicting a class label of x by combining the multiple learners and obtaining total vote received by each class with averaging their values (as a weighted sum),

$$yi(x) = \sum_{t=1}^{T} w_t h_{ti} \quad i = 1, \ldots m, w_t \geq 0, \sum_{t=1}^{T} w_t = 1,$$

(w_t is the weight assigned to the t-*th* classifier h_t according to some measure of performance)

3. Returning the class label with choosing the class that receives the highest total vote (weighted majority voting) as the final ensemble decision. Specifically, y_{Final} (x) = argmax y_i(x).

In the following, the executive stages of the proposed model and the results are presented.

Materials and methods

Research methodology

The general block diagram of the proposed model is shown in Fig. 1. This diagram consists of three major components. To build the proposed classifier, we use the machine learning ensemble meta-algorithm and convert weak learners to strong ones. In the first component, after preparing and preprocessing the data, multiple well-known supervised algorithms are constructed using CRISP methodology [27] to classify control level. In this paper, multinomial logistic regression, support vector machine, random forest, extreme gradient boosting, K-nearest neighbor, decision tree, and Gaussian naïve Bayesian are used as seven supervised algorithms.

Multinomial logistic regression (MLR), Support vector machine (SVM), Random forest (RF), Extreme gradient boosting (XGB), K-nearest neighbor (KNN), Decision Tree (DT), Gaussian Naïve Bayesian (GNB), Feature Selection (FS), Multivariate adaptive regression splines (MARS), Recursive Feature Elimination (RFE), Information gain (IG), Mean decrease in Gini (MDG), Mean decrease in accuracy (MDA).

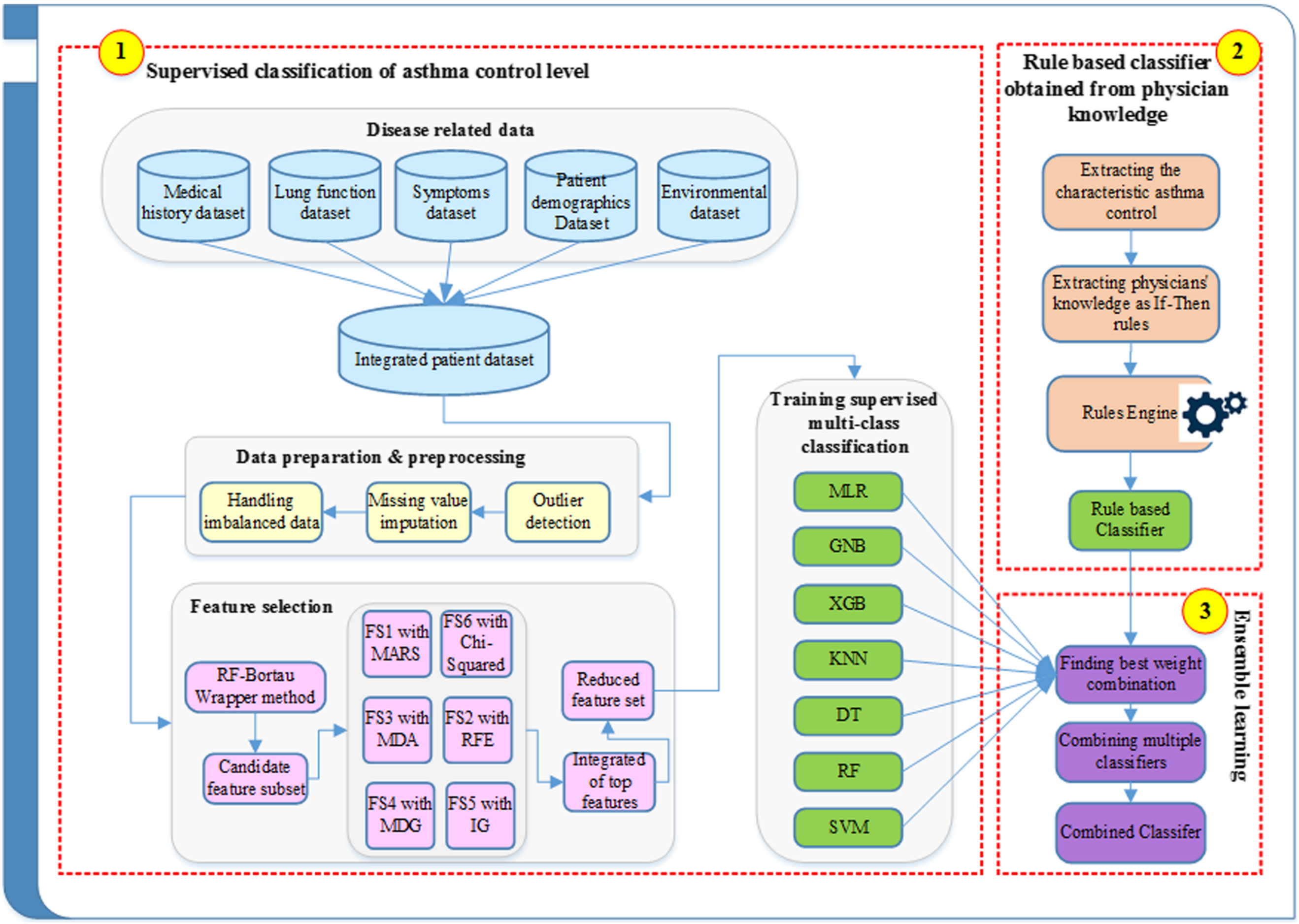

Fig. 1 Detailed architecture of proposed ensemble learning for asthma control level detection

In the second component, a rule-based classifier (RBC) is made up. RBC is based on rules derived from the physicians' knowledge to classify asthma control level. For this purpose, it is necessary to be extracted the characteristics and instructions that physicians consider to assess the level of control. **Table 2** shows these characteristics and instructions. These instructions are transformed into if-then rules, stored in a rule engine and then used in the form of a rule-based classifier in our ensemble model. Physicians assess four types of characteristics including daytime symptoms, nighttime symptoms, level of activity and need for Reliever use simultaneously and then detect control level based on **Table 2** [28]. According to RBC, a data record is labeled "well-controlled" when none of the characteristics are met.

Table 2 The characteristics and rules used by physicians to classify the level of asthma control.*So rated when none of characteristics are met.***So rated when at least 3 of the characteristics are met in any week.**So rated when 1 or 2 of the characteristics are met in any week

In the past week, has the patient had:	**Well controlled level***	**Not well controlled level****	**Very poorly controlled level*****
1. Daytime asthma symptoms more than twice a week? Yes ☐ No ☐ 2. Any night waking due to asthma? Yes ☐ No ☐ 3. Reliever needed for symptoms more than twice a week? Yes ☐ No ☐ 4. Any activity limitation due to asthma? Yes ☐ No ☐	None of these	1-2 of these	3-4 of these

Table 3 Attributes list of our dataset

Variable Groups	Attributes	Codes	Possible values	Missing values (%)
Patient demographics	Patient's age at registration	AGE	Numerical (years)	…
	Date of referral to Asthma & Allergy Clinic	DATE	Numerical (Date)	…
	Gender	GENDER	Male, Female	…
	Weight	WEIGHT	Numerical (kg)	…
	Height	HEIGHT	Numerical (cm)	…
	Body mass index	BMI	Numerical (kg/m^2)	…
	Ethnicity	ETHNIC	Categorical	…
	Birthplace	BIRTHPLACE	Categorical	…
	Occupation	OCCUP	Categorical	…
	Education	EDUC	Categorical	…
Lung Function	Pre bronchodilator expiratory Forced Vital Capacity (FVC)	FVC_PRE	Numerical	4.16
	Predicted FVC	FVC_PRED	Numerical	4.16
	Pre bronchodilator FVC/ predicted FVC ratio	FVC_PREPRED%	Numerical (%)	4.16
	Post bronchodilator FVC/ predicted FVC ratio	FVC_POSTPRED%	Numerical (%)	4.16
	Post bronchodilator FVC/ Pre bronchodilator FVC ratio	FVC_POST%PRE	Numerical (%)	4.16
	Pre bronchodilator Forced Expiratory Volume in one second (FEV_1)	FEV1_PRE	Numerical	4.16
	Predicted FEV_1	FEV1_PRED	Numerical	4.16
	Post bronchodilator FEV_1	FEV1_POST	Numerical	4.16
	Pre bronchodilator FEV_1/ predicted FEV_1 ratio	FEV1_PREPRED%	Numerical (%)	4.16
	Post bronchodilator FEV_1/ predicted FEV_1 ratio	FEV1_POSTPRED%	Numerical (%)	4.16
	Post bronchodilator FVC/ Pre bronchodilator FVC ratio	FEV1_POST%PRE	Numerical (%)	4.16
	Pre bronchodilator FEV_1/FVC ratio	FEV1/FVC%_PRE	Numerical (%)	4.16
	Predicted FEV_1/FVC ratio	FEV1/FVC%_PRED	Numerical (%)	4.16
	Post bronchodilator FEV_1/FVC ratio	FEV1/FVC%_POST	Numerical (%)	4.16
	Pre bronchodilator FEV_1/FVC / predicted FEV_1/FVC ratio	FEV1/FVC%_PREPRED%	Numerical (%)	4.16
	Post bronchodilator FEV_1/FVC / predicted FEV1/FVC ratio	FEV1/FVC%_POSTPRED%	Numerical (%)	4.16
	Post bronchodilator FEV_1/FVC / Pre bronchodilator FEV_1/FVC ratio	FEV1/FVC%_POST%PRE	Numerical (%)	4.16
	Pre bronchodilator Peak Expiratory Flow (PEF)	PEF_PRE	Numerical	4.16
	Predicted PEF	PEF_PRED	Numerical	4.16
	Post bronchodilator PEF	PEF_POST	Numerical	4.16
	Pre bronchodilator PEF / predicted PEF ratio	PEF_PREPRED%	Numerical (%)	4.16
	Post bronchodilator PEF / predicted PEF ratio	PEF_POSTPRED%	Numerical (%)	4.16
	Post bronchodilator PEF / Pre bronchodilator PEF ratio	PEF_POST%PRE	Numerical (%)	4.16
Symptoms	PEF rate obtained on arising in the morning	PEFR_MORN	Numerical (L/min)	6.49
	PEF rate obtained just before bedtime	PEFR_EVEN	Numerical (L/min)	7.76
	Did you use quick-relief-inhaler during the last 24 h?	MED_AP	Yes, no	5.88
	Did you have shortness of breath in the last 24 h?	SHORT_BREA_AP	Yes, no	5.88
	Did you have wheezing in the last 24 h?	WHEE_AP	Yes, no	5.88
	Did you have coughing in the last 24 h?	COUG_AP	Yes, no	5.88
	Did you have Tight chest in the last 24 h?	TIGHT_CHEST_AP	Yes, no	5.88
	Did you have pain in the last 24 h?	PAIN_AP	Yes, no	5.88
	Did you have limitation of physical activities in the last 24 h?	PHYS_ACT_AP	Yes, no	5.88
	Did you have night time awakening during the last night?	AWAK_AP	Yes, no	5.88
	Asthma control test (ACT score)	ASTH_CONT	Not well-controlled, Very poorly-controlled, Well-controlled	2.05
Environmental factors Pollution data	Daily CO	CO	Numerical (ppb)	12.43

Table 3 (continued)

		Daily O_3	O3	Numerical (ppb)	11.28
		Daily NO_2	NO2	Numerical (ppb)	11.28
		Daily SO_2	SO2	Numerical (ppb)	10.41
		Daily PM_{10}	PM10	Numerical (μg/m^3)	10.06
		Daily $PM_{2.5}$	PM2.5	Numerical (μg/m^3)	8.85
		Air quality index	AQI	Numerical	8.18
		Daily air quality status	AIR_QUAL	Good, Moderate, Unhealthy for Sensitive Groups, Unhealthy, Hazardous	8.18
	Wheatear data	Daily max air temperature	T_MAX	Numerical (°C)	1.49
		Daily mean air temperature	T_AVG	Numerical (°C)	0.01
		Daily min air temperature	T_MIN	Numerical (°C)	1.63
		Dew point	DEWPOINT	Numerical (°C)	1.35
		Relative humidity level	HUMID	Numerical (%)	1.35
		Atmospheric pressure	PRESS	Numerical	1.56
		Daily wind speed	WIND	Numerical(m/s)	2.05
		Total daily precipitation	PRECIP	0(mm)	1.95
		Atmospheric events	ATMO_EVE	Fog, rain, snow, sunny, thunderstorm	2.12
Medical History	Clinical variables	Disease duration	DISE_DURE	Numerical	…
		Number of cigarettes smoked per day	NUM_SMOKE	Numerical	…
		Coughing	COUGH	Yes, no	…
		Wheezing	WHEEZE	Yes, no	…
		Shortness of breath	SHORT_BREA	Yes, no	…
		Nighttime symptoms	NIGHT_SYMP	Yes, no	…
		Daytime symptoms	DAY_SYMP	Yes, no	…
		Trigged with activity and emotional states	ACT_EMOT_SYS	Yes, no	…
		Sputum	SPUTUM	Yes, no	…
		Chest tightness	CHES_TIGHT	Yes, no	…
		Snoring	SNOR	Yes, no	…
		Types of symptoms	TYPE_SYS	categorical	…
		Allergy season	ALLG_SEAS	Winter, spring, summer, fall	…
		Non allergic disease	NONE_ALLG_DISE	Yes, no	…
		Allergic disease	ALLG_DISE	Yes, no	…
		Hospitalization due to asthma exacerbations	HOSP_EXAC	Yes, no	…
		Asthma severity	ASTH_SEV	Intermittent, mild, moderate, sever	…
	Co-morbidities	History of influenza vaccine injection	INFLU_VACC	Yes, no	…
		Allergic Bronchopulmonary Aspergillosis (ABPA)	CO_ABPA	Yes, no	…
		Chronic stress	CO_CHOR_STRE	Yes, no	…
		Gastroesophageal reflux disease (GERD)	CO_GERD	Yes, no	…
		Obesity	CO_OBES	Yes, no	…
		Chronic obstructive pulmonary disease (COPD)	CO_COPD	Yes, no	…
		Vocal cord dysfunction (VCD)	CO_VCD	Yes, no	…
		Obstructive sleep apnea	CO_OSA	Yes, no	…
		Sinusitis	CO_SINUS	Yes, no	…
		Nasal polyps	CO_NASAL_POLY	Yes, no	…
		Cardiovascular	CO_CARD	Yes, no	…
	Asthma triggers	Depression	CO_DEP	Yes, no	…
		Respiratory infections	RES_INF_TRIG	Yes, no	..
		Exercise and physical activity	EXEC_ACT_ TRIG	Yes, no	…
		Perfume and cologne	PERF_COL_ TRIG	Yes, no	…

Table 3 (continued)

	Detergent and bleach	DET_BLEA_ TRIG	Yes, no	…
	Stove and appliances	STOV_APPL_ TRIG	Yes, no	…
	Flowers and plants	FLOW_PLAN_ TRIG	Yes, no	…
	Air pollution	AIR_POLL_ TRIG	Yes, no	…
	Cold weather	COLD_WEAT_ TRIG	Yes, no	…
	Climate change	CLIM_CHAN_ TRIG	Yes, no	…
	Emotional states	EMO_STAT_ TRIG	Yes, no	…
	Menstrual cycle	MENS_CYC_ TRIG	Yes, no	…
	Animals and insects	ANIM_INS_ TRIG	Yes, no	5.2
	Household dusts	HOUS_DUS_ TRIG	Yes, no	5.2
	Mushrooms and molds	MUSH_MOL_ TRIG	Yes, no	5.2
	Smoking	SMOK_ TRIG	Yes, no	…
	Occupational allergies	OCCUP_ALLG	Yes, no	…
Allergy history	Exposure to tobacco smoke	EXPO_TOBAC	Yes, no	5.2
	Allergies to wheat	ALLG_WHE	Yes, no	5.2
	Allergies to milk	ALLG_MILK	Yes, no	5.2
	Allergies to eggs	ALLG_EGGS	Yes, no	5.2
	Allergies to soy	ALLG_SOY	Yes, no	5.2
	Allergies to peanuts	ALLG_PEA	Yes, no	5.2
	Allergies to fish	ALLG_FISH	Yes, no	5.2
	Allergies to shellfish	ALLG_SHEL	Yes, no	5.2
	Allergies to eggplant	ALLG_EGGP	Yes, no	5.2
	Allergies to nuts	ALLG_NUTS	Yes, no	5.2
	Allergies to tomatoes	ALLG_TOM	Yes, no	5.2
	Allergies to spices	ALLG_SPI	Yes, no	5.2
	Allergies to fried foods	ALLG_FRI	Yes, no	5.2
	Allergies to kiwi	ALLG_KIWI	Yes, no	5.2
	Drug allergies to penicillin	DRUG_ALLG_PEN	Yes, no	…
	Drug allergies to cotrimoxazole	DRUG_ALLG_COTR	Yes, no	…
	Drug allergies to amoxicillin	DRUG_ALLG_AMO	Yes, no	…
	Drug allergies to aspirin	DRUG_ALLG_ASP	Yes, no	…
	Drug allergies to NSAIDs	DRUG_ALLG_NSA	Yes, no	…
History of allergic diseases	Food allergy	ALLG_FOOD	Yes, no	5.2
	Eczema	ECZEMA	Yes, no	…
	Skin dryness	SKIN_DRY	Yes, no	…
	Nasal allergy	ALLG_NASAL	Yes, no	…
	Hives	HIVES	Yes, no	…
	Drug allergies	DRUG_ALLG	Yes, no	…
	Allergy to the bites of insects	ALLG_INS	Yes, no	…
	Anaphylaxis	ANAPHYLAXIS	Yes, no	…
Family history	Eye allergies	ALLG_EYE	Yes, no	…
	Family ‘s allergic diseases	FAM_ALLG_DIS	Yes, no	…
	Family ‘s asthma	FAM_ASTH	Yes, no	…
	Family ‘s hives	FAM_HIVES	Yes, no	…
	Family ‘s rhinitis	FAM_RHIN	Yes, no	…
	Family ‘s drug Allergies	FAM_ DRUG_ALLG	Yes, no	…
	Family ‘s eczema	FAM_ECZ	Yes, no	…

Therefore, only one rule is defined to detect "well-controlled" class. Also, a data record is labeled "Not well-controlled" when 1 or 2 of the characteristics are met in any week. Therefore, ten rules are defined to recognize "Not well-controlled" class. Finally, a data record is labeled "very poorly-controlled" when at least 3 characteristics out of 4 items are met in any week. Therefore, five rules are defined to detect "very poorly-controlled" class. As a result, the rules engine has a total of 16 rules for categorizing the level of asthma control. In this research, RBC was encoded at a rule engine using *Drools* and combined to our proposed ensemble learning.

In the third component, all classifiers are combined to create multiclass ensemble learning for asthma control level detection. Firstly, we find the best weight combination for single classifiers and then apply the weight values into each probability to create a combined classifier. Before building such powerful models, selecting a base model is essential to compare the performance of the newly built model. In this paper, MLR is used as the base model.

Data collection

This study was conducted in cooperation with Iranian National Research Institute of Tuberculosis and Lung Disease, and the required data (included five stimuli groups) were collected from 96 asthmatic patients (>5 years old) referring to the Asthma and Allergy Clinic within a 9-month period. Table 3 shows the research variables, their possible values, and the corresponding codes.

For this purpose, variables and parameters of the two groups of demographic data and medical history were collected using a standard registry form when the patient referred to the clinic. Allergy skin test and the patients' lung function (using Spirometry test), were collected in a dataset.

There are several efficient tools such as peak flow meter and asthma control test questionnaire, which have been developed for monitoring and controlling of asthma [29]. To this end, for 4–12 consecutive weeks, the patients were asked to measure and write down their peak expiratory flow rate (PEFR) daily at the morning and afternoon times using a peak flow meter. Moreover, the data of other daily symptoms of asthma were collected with the help of ACT [7], the ACT scores of each patient were calculated within the weekly periods.

In addition, the environmental stimuli such as the air pollution parameters and daily meteorology information were needed for each data record in view of date and address of patients' place of residence. The air pollutant parameters were obtained from 24 pollution-monitoring stations of Tehran Air Quality Control Company. Moreover, the meteorology parameters were extracted from four synoptic stations of the Meteorological Organization. Then they were connected to each patient's data record with the help of *ArcGIS* software.

Finally, the final dataset includes one multivariate dataset and a three-class response variable with labels of well-controlled, not well-controlled and very poorly-controlled levels. This information was obtained from 96 patients with a total of 2870 records collected base on daily assessment of asthma control.

Implementation of the method

Data pre-processing

In this study, outlier detection, handling the missing values and re-sampling for imbalanced classes were used for data pre-processing.

To review the outliers, we used a multivariate model approach, named "Cook's distance" [30] and eliminated them from the dataset after further review, if necessary. To address the problem of missing values, we used multiple imputation using the fully conditional specification method [31] for filling the empty cells. After these stages, the final dataset included 140 variables and 2870 observations.

As Table 4 shows, on the original dataset, 65.43, 33.24 and 1.32% of the samples belong to the well-controlled, not well-controlled and very poorly-controlled classes, respectively, indicating the classes' imbalance. To fix this challenge, we created the datasets 2 and 3 with an oversampling method [32], namely Randoverclassif, and Synthetic Minority Oversampling Technique [33], namely Smotclassif, respectively. Dataset No.1 is also an unbalanced dataset.

Feature selection

Different feature selection algorithms yield different candidate feature subset and, features with the lowest ranking values of various indices in most methods can be safely rejected. Furthermore, it is necessary to be used methods that eliminate redundant and correlated features. Therefore, we have applied a hybrid approach by combining various feature selection methods to determine the best subset of features. This approach has provided maximum information about the asthma control level detection and no important variables have missed.

For this purpose, we created a feature subset using a wrapper approach called Boruta. This method divides the features into three categories of confirmed, tentative, and rejected variables. Out of the 140 initial variables, 121 and 19 variables were confirmed and rejected, respectively. In the next step, feature selection was implemented using other methods on 121 confirmed variables separately. Then we integrated the top joint variables in all methods, of which 35 variables were chosen as the selected variables. Six methods were as below:

Table 4 The main and balanced datasets

Datasets	Data size	Data with well-controlled class	Data with not well-controlled class	Data with very poorly-controlled class
Dataset Number 1 (D_1)	2870	1878 (65.43%)	954 (33.24%)	38 (1.32%)
Dataset Number 2 (D_2)	3945	1315 (33.33%)	1315 (33.33%)	1315 (33.33%)
Dataset Number 3 (D_3)	2068	670 (32.39%)	699 (33.80%)	699 (33.80%)

1. Multivariate adaptive regression splines (MARS) method measuring the importance of variables with generalized cross-validation and residual sum of squares [34].
2. Recursive feature elimination (RFE) measuring the importance of variables by 10-fold cross-validation [35].
3. Random forest algorithm with the function scoring of mean decrease in accuracy (MDA) [36].
4. Random forest algorithm with the function scoring of mean decrease in Gini (MDG) [36].
5. An entropy-based method with information gain (IG) [37].
6. Pearson's Chi-square test [38].

After feature selection, our reduced dataset included 2870 observations and 35 variables. Fig. 2 shows the selected variables and their importance.

Creating and evaluating the ensemble learning model

To build the ensemble learning model (defined in sections 1.2 and 2.1), it required various types of models with weights on each model. In this study, MLR, XGB, RF, DT, KNN, GNB, SVM, and RBC were used as base learners. In the first step, these algorithms were created using 5-fold cross-validation separately. In addition, 20 independent runs of 5-fold cross-validation were performed to deal with any biasing that might have occurred during the random partitioning process. It is to be noted that all supervised models have encoded with *Rstudio* software.

In the next step, our ensemble model was built by multiple outputs from various types of the machine learning models with proper weights on each output; however, choosing

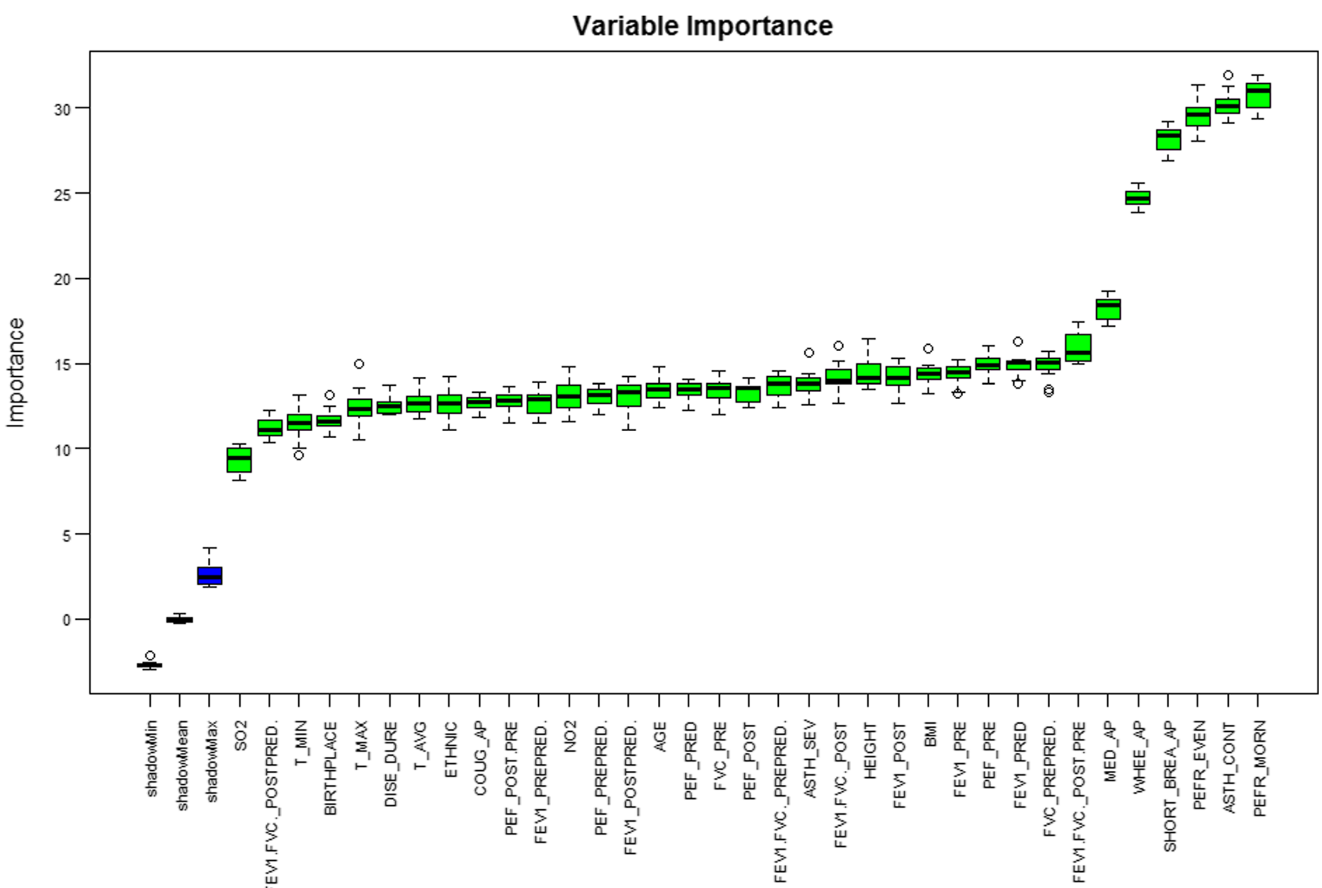

Fig. 2 Reduced features subset and their importance

<table>
<tr><td colspan="2" rowspan="2">Confusion Matrix</td><td colspan="3">Predicted level of asthma control</td></tr>
<tr><td>Class 1:
Very poorly controlled level</td><td>Class 2:
Not well controlled level</td><td>Class 3:
Well controlled level</td></tr>
<tr><td rowspan="3">Actual level of asthma control</td><td>Class 1:
Very poorly controlled level</td><td>A</td><td>B</td><td>C</td></tr>
<tr><td>Class 2:
Not well controlled level</td><td>D</td><td>E</td><td>F</td></tr>
<tr><td>Class 3:
Well controlled level</td><td>G</td><td>H</td><td>I</td></tr>
</table>

True positives (TP) True negatives (TN) Misclassified cases (FP, FN)

❖ True Positives (TP): The label belongs to the class, and it is correctly predicted.
❖ True Negative (TN): The label does not belong to the class, and it is correctly predicted.
❖ False Positives (FP): The label does not belong to the class, but classifier predicted as positive.
❖ False Negative (FN): The label belongs to the class but is predicted as negative.

Fig. 3 The 3-class confusion matrix

perfect combination of the optimal weights was another challenge. Although there were many different methods to choose the optimal weights, this study has used the brute force search with multiple for-loops. Brute-force search involved systematically enumerating all possible candidates for checking whether each candidate was able to satisfy the condition of the problem. In here, all possible candidates of different combination of weights in the range of [0, 0,05, …, 0.95, 1] were applied to each classifier with multiple loops. It is to be noted that, the sum of the weights applied to classifiers should be equal to 1 in each iteration. Being an iterative process, the accuracy of all possible ensemble model was calculated and the ensemble that acquired the best performance was selected as the best learner for asthma control level detection and its weights were chosen as optimal weights and applied into each probability.

In this study, two ensemble models were trained on two different datasets (D_2, and D_3):

- The first ensemble model combining seven supervised algorithms
- The second ensemble model combining seven supervised algorithms as well as the rule-based classifier

After creating models, five standard metrics including accuracy, recall, specificity, precision, and negative predictive value (NPV), were used to measure the models' performance using 3-class confusion matrix (Fig. 3) [39].

Measures for multi-class classification are based on a generalization of the measures of binary classification for many classes C_i [39]. For an individual class C_i, the assessment is defined by TP_i, FN_i, TN_i, FP_i (For instance, for class 1, FN_i is the number of instances of very poorly-controlled level that the model incorrectly identifies as not well-controlled or well-controlled). Therefore, for the above three-way confusion matrix, the following three one-versus-all matrices (Fig. 4) are returned to calculate five standard metrics for each class separately [39].

Also, the quality of the overall classification is assessed using a micro-averaged accuracy that aggregates the contributions of all classes to compute the average metric. In a multi-class classification setup, micro-average is preferable if there is class imbalance problem and is computed using Fig. 4 and below formula:

$$Micro\text{-}averaged\ accuracy = \frac{\sum_{i=1}^{3} \frac{TP_i + TN_i}{TP_i + TN_i + FP_i + FN_i}}{3} =$$
$$\frac{1}{3}\left[\left(\frac{A + (E+F+H+I)}{A + (E+F+H+I) + (B+C) + (D+G)}\right)_{Class\ 1} + \left(\frac{E + (A+I+C+G)}{E + (A+I+C+G) + (D+F) + (B+H)}\right)_{Class\ 2} + \left(\frac{I + (A+B+E+D)}{I + (A+B+E+D) + (G+H) + (C+F)}\right)_{Class\ 3}\right]$$

Concerning the classification of asthma control level, it is important to properly detect the cases with not well-controlled and very poorly-controlled classes rather than the cases with well-controlled class. If the case with very-poorly controlled level is diagnosed wrongly as the not well-controlled or well-

<table>
<tr><td colspan="4">Very poorly controlled level-vs-All</td></tr>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Predicted level of asthma control</td></tr>
<tr><td>Class1</td><td>Other</td></tr>
<tr><td rowspan="2">Actual level of asthma control</td><td>Class1</td><td>A</td><td>B+C</td></tr>
<tr><td>Other</td><td>D+G</td><td>E+F+H+I</td></tr>
</table>

<table>
<tr><td colspan="4">Not well controlled level-vs-All</td></tr>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Predicted level of asthma control</td></tr>
<tr><td>Class2</td><td>Other</td></tr>
<tr><td rowspan="2">Actual level of asthma control</td><td>Class2</td><td>E</td><td>D+F</td></tr>
<tr><td>Other</td><td>B+H</td><td>A+I+C+G</td></tr>
</table>

<table>
<tr><td colspan="4">Well controlled level-vs-All</td></tr>
<tr><td colspan="2" rowspan="2"></td><td colspan="2">Predicted level of asthma control</td></tr>
<tr><td>Class3</td><td>Other</td></tr>
<tr><td rowspan="2">Actual level of asthma control</td><td>Class3</td><td>I</td><td>G+H</td></tr>
<tr><td>Other</td><td>C+F</td><td>A+B+E+D</td></tr>
</table>

True positives (TP) True negatives (TN) Misclassified cases (FP, FN)

Fig. 4 One-versus-all confusion matrix for 3-class classification

Table 5 Performance evaluation of the models used in asthma control level detection

Performance Evaluation		Multinomial Logistic Regression		Xgboost Method		Gaussian NB		K-Nearest Neighbor		Support Vector Machine	
		D_2	D_3	D_2	D_3	D_2	D_3	D_2	D_3	D_2	D_3
Recall	Well-controlled zone	0.861	0.856	0.891	0.899	0.869	0.867	0.817	0.852	0.89	0.887
	Not-well controlled zone	0.813	0.846	0.881	0.835	0.599	0.603	0.769	0.739	0.775	0.711
	Very poorly-controlled zone	0.647	0.727	0.805	0.728	0.161	0.138	0.318	0.222	0.273	0.211
Specificity	Well-controlled zone	0.921	0.861	0.888	0.851	0.635	0.63	0.753	0.755	0.78	0.728
	Not-well controlled zone	0.938	0.931	0.92	0.939	0.81	0.806	0.884	0.869	0.887	0.874
	Very poorly-controlled zone	0.979	0.976	0.935	0.935	0.958	0.956	0.955	0.954	0.998	0.996
Precision	Well-controlled zone	0.837	0.822	0.843	0.803	0.717	0.734	0.757	0.756	0.756	0.715
	Not-well controlled zone	0.816	0.806	0.839	0.811	0.673	0.659	0.706	0.771	0.723	0.685
	Very poorly-controlled zone	0.739	0.707	0.616	0.616	0.658	0.707	0.636	0.545	0.698	0.627
Neg Pred Value	Well-controlled zone	0.916	0.899	0.866	0.92	0.838	0.832	0.869	0.849	0.835	0.838
	Not-well controlled zone	0.936	0.898	0.916	0.887	0.775	0.793	0.855	0.85	0.889	0.847
	Very poorly-controlled zone	0.984	0.976	0.959	0.958	0.945	0.941	0.982	0.975	0.972	0.965
Accuracy	Well-controlled zone	0.823	0.799	0.879	0.847	0.772	0.779	0.865	0.853	0.815	0.768
	Not-well controlled zone	0.806	0.839	0.881	0.867	0.724	0.73	0.841	0.834	0.761	0.722
	Very poorly-controlled zone	0.773	0.792	0.875	0.837	0.579	0.567	0.657	0.608	0.605	0.573
Performance Evaluation- Continued		**Random Forest**		**Tree-based Model**		**Rule-based classifier**		**Ensemble Learning 1**		**Ensemble Learning 2 (Proposed)**	
		D_2	D_3	D_2	D_3	D_2	D_3	D_2	D_3	D_2	D_3
Recall	Well-controlled zone	0.897	0.889	0.878	0.88	0.872	0.859	0.905	0.917	0.906	0.883
	Not-well controlled zone	0.853	0.809	0.828	0.754	0.768	0.791	0.895	0.866	0.818	0.838
	Very poorly-controlled zone	0.815	0.77	0.667	0.286	0.879	0.861	0.698	0.756	0.908	0.872
Specificity	Well-controlled zone	0.899	0.852	0.88	0.757	0.934	0.942	0.929	0.891	0.963	0.949
	Not-well controlled zone	0.906	0.915	0.924	0.904	0.905	0.888	0.944	0.932	0.936	0.927
	Very poorly-controlled zone	0.975	0.976	0.994	0.996	0.916	0.922	0.989	0.997	0.915	0.920
Precision	Well-controlled zone	0.827	0.857	0.858	0.824	0.868	0.875	0.887	0.882	0.927	0.894
	Not-well controlled zone	0.793	0.834	0.846	0.815	0.817	0.798	0.866	0.896	0.876	0.860
	Very poorly-controlled zone	0.656	0.707	0.595	0.727	0.827	0.838	0.819	0.767	0.822	0.840
Neg Pred Value	Well-controlled zone	0.899	0.923	0.862	0.859	0.937	0.934	0.936	0.934	0.952	0.943
	Not-well controlled zone	0.931	0.903	0.93	0.868	0.876	0.884	0.936	0.938	0.903	0.915
	Very poorly-controlled zone	0.996	0.998	0.996	0.976	0.943	0.934	0.996	0.996	0.958	0.937
Accuracy	Well-controlled zone	0.868	0.854	0.824	0.758	0.914	0.915	0.873	0.889	0.943	0.927
	Not-well controlled zone	0.82	0.812	0.801	0.789	0.857	0.853	0.896	0.859	0.894	0.897
	Very poorly-controlled zone	0.825	0.818	0.798	0.641	0.904	0.902	0.844	0.835	0.913	0.904

controlled case, it is likely that due to providing inappropriate treatment, the patient will suffer from further asthma attacks and serious control status. Furthermore, if the class of not well-controlled is wrongly diagnosed as the well-controlled one, due to insufficient adjustment of the treatment program, the patient may fall into the very poorly-controlled level and thus inappropriate consequences are brought about. For this reason, improvements of results in the classification of not well-controlled and very poorly-controlled classes are more important than the well-controlled one.

In models evaluation section, considering the accuracy metric is not sufficient because in datasets with the problem of imbalanced classes, the results would be deceptive, while the classification model does not detect any transaction involving a minority class [40]. In such cases, improvement of two metrics of recall and accuracy is more important in uncontrolled classes. It is also required to decrease the number of wrong alarms. Hence, the value of precision should be improved.

Results and discussion

Table 5 shows the results obtained from implementation of each single classifier, the rule-based classifier, and the ensemble learning models 1 and 2.

All single classifiers in the well-controlled zone classification have almost similar and acceptable results in two datasets. GNB has weak performance for not well-controlled zone classification, while RF and XGB yield acceptable results for this class on both datasets. RF and XGB classifiers have acceptable accuracy and recall to detect very poorly-controlled class. While the results from other algorithms are undesirable, it is very disappointing in SVM, KNN, DT and GNB models. In KNN, SVM and XGB, the precision for the very poorly-controlled class has no acceptable results on D_2 and D_3, and if used, it will increase wrong alarms for occurrence of this class. Generally, the single algorithms on D_2 have better performance than on D_3. Also, the accuracy, precision, and recall of “perform the best as a single model.

Table 6 shows the weight distribution obtained from finding best weight values combination on each prediction that was applied into each probability in ensemble learning models 1 and 2. As indicated, RBC, RF, and SVM have the highest weight in the ensemble learning model 2, respectively. It is interesting to see some bad model such as SVM is contributing more weight than better models such as XGB. By comparison between the base model (MLR), and the proposed ensemble model 2, the accuracy on D_2 for well-controlled zone (over 14%), for not well-controlled zone (over 10%) and for very poorly-controlled zone (over 18%) are improved. The ensemble model 2 performs the best out of all models with accuracy of 0.943 for well-controlled zone, 0.894 for not well-controlled zone and 0.913 for very poorly-controlled zone on D_2.

It is to be noted that, the rule-based classifier has better results than single classifiers and while combining with multiple models, the performance of asthma control level detection is improved especially for very poorly-controlled and not well-controlled zones. The quality of the overall classification of asthma control detection models in Fig. 5 shows that proposed model has yielded better results than other algorithms and the micro averaged-accuracy index is estimated as 91.66% on D_2.

Conclusions

The present study was designed to develop a novel ensemble learning method for asthma control level detection using the combination of supervised learners with rule-based classifier. The rule-based classifier was created using the physicians' knowledge and stored in a rule engine. The proposed model, in comparison with the other classifiers, significantly improved the recall, precision and accuracy metrics, especially for very poorly-controlled class. The reasons can be integrating experts' knowledge with ensemble learning, feature selection, balancing operation on the dataset, and use of various variables affecting the asthma control level. Also, the results showed that machine learning techniques such as ensemble learning have high potential to be used in prognostic systems for asthma control level detection especially when combined with medical knowledge. In future research, numerous objectives can be considered as follows:

- Adding other factors affecting asthma control level such as genetic factors and biomarkers to enhance the performance of asthma control level detection
- Implementing the asthma control level detection models with time series approach rather than using the attribute-based data

Table 6 Ensemble model weight

Classifiers	MLR	XGB	GNB	KNN	SVM	RF	DT	RBC
Ensemble model 1	0.05	0	0	0	0.05	0.90	0	–
Ensemble model 2 (Proposed)	0.05	0.05	0	0	0.2	0.3	0	0.4

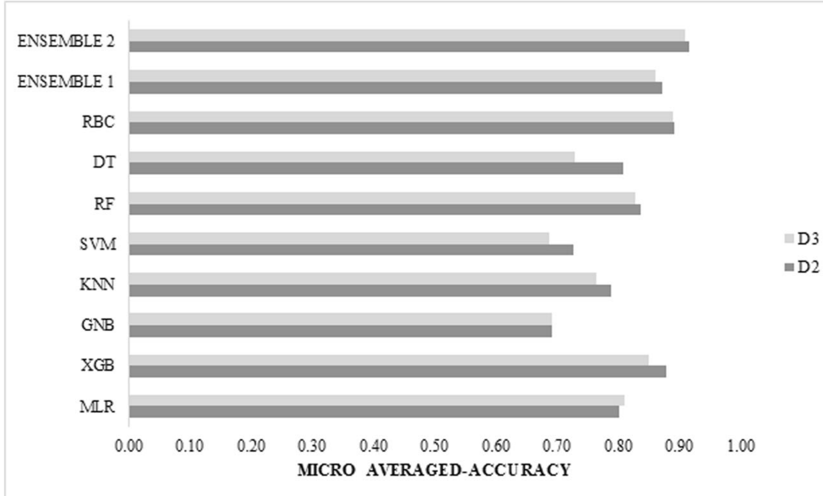

Fig. 5 Comparison of accuracy of the classification models in two datasets

- Using the capabilities of novel technology to create self-care systems with the aid of the models of asthma control level detection

Compliance with ethical standards

Conflicts of interest None.

Ethical approval None.

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