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A hybrid intelligent system for diagnosing microalbuminuria in type 2 diabetes patients without having to measure urinary albumin

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ABSTRACT

Microalbuminuria (MA) is an independent predictor of cardiovascular and renal disease, development of overt nephropathy, and cardiovascular mortality in patients with type 2 diabetes. Detecting MA is an important screening tool to identify people with high risk of cardiovascular and kidney disease. The gold standard to detect MA is measuring 24-h urine albumin excretion. A new method for MA diagnosis is presented in this manuscript which uses clinical parameters usually monitored in type 2 diabetic patients without the need of an additional measurement of urinary albumin. We designed an expert-based fuzzy MA classifier in which rule induction was performed by particle swarm optimization. A variety of classifiers was tested. Additionally, multiple logistic regression was used for statistical feature extraction. The significant features were age, diabetic duration, body mass index and HbA1C (the average level of blood sugar over the previous 3 months, which is routinely checked every 3 months for diabetic patients). The resulting classifier was tested on a sample size of 200 patients with type 2 diabetes in a cross-sectional study. The performance of the proposed classifier was assessed using (repeated) holdout and 10-fold cross-validation. The minimum sensitivity, specificity, precision and accuracy of the proposed fuzzy classifier system with feature extraction were 95%, 85%, 84% and 92%, respectively. The proposed hybrid intelligent system outperformed other tested classifiers and showed "almost perfect agreement" with the gold standard. This algorithm is a promising new tool for screening MA in type-2 diabetic patients.

1. Introduction

Diabetes mellitus is a group of metabolic diseases. A diabetic patient has high blood sugar, either because not enough insulin is produced by the pancreas, or because cells do not respond to the produced insulin [1]. Worldwide, 347 million people had diabetes in 2011 and by 2030 this number will increase to 552 million. Diabetes caused 4.6 million deaths in 2011 and is projected to be the 7th leading cause of death in 2030 according to the WHO. More than 80% of diabetes deaths occur in low- and middle-income countries [2]. Type 2 diabetes, the most common form of diabetes, results from the body's inefficient use of insulin and causes at least 90% of all cases of diabetes. Diabetic 2 patients have high risk of a variety of complications, basically because of complicated and interconnected mechanisms such as hyperglycemia, insulin-resistance, and accelerated atherogenesis. [3]. Life threatening cardio-cerebrovascular disease such as coronaropathy, stroke and heart failure are also associated with type 2 diabetes.

Microalbuminuria (MA) is one of the first clinical indicators of microvascular damage in diabetes [4]. MA is defined as a persistent elevation of albumin in the urine of >30 to <300 mg/d (>20 to <200 μg/min). The acceptable amount of albumin in the urine is less than 30 mg/d; values above 300 mg/d (200 μg/min) indicate overt proteinuria (macroalbuminuria). The underlying association between MA and the development of diabetic complications has been well established in the literature [5]. In fact, MA is a well-known predictor of renal disease and consequent progress of overt diabetic nephropathy in patients with type 2 diabetes [6,7]. It has also been shown that MA predicts silent myocardial ischemia, polyvascular diseases, and increased (cardiovascular)

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mortality in type 2 diabetes patients. Considering the high incidence of MA (approximately 40%) in patients with type 2 diabetes [8] and its significant association with cardiovascular and renal events, its screening and intervention measures are very important.

Studies have shown that many disorders, such as hyperglycemia, hypertension, and obesity in diabetic patients are associated with an increased risk of MA [9]. Also, several studies have revealed that the risk of MA depends on multiple factors, including age, gender, BMI (body mass index), DD (diabetic duration), BP (blood pressure), FBS (fasting blood sugar), HbA1c (the average percentage level of blood glucose over the previous 3 months), Bs2hpp (2 h post-prandial blood glucose), CHOL (total cholesterol), LDL (low-density lipoprotein), HDL (high-density lipoprotein), and TG (triglyceride) [10]. Previous studies on the relationship between various risk factors and MA have provided controversial results. In the literature, linear regression methods were usually used for analyzing the risk factors of MA. They include either univariate methods (the correction between the factor and the outcome) or multivariate ones (multiple linear regressions). Univariate methods do not consider the interaction between different factors. Multivariate techniques, on the other hand, depend on several assumptions, including the linearity in the underlying system or the normality of the response variable, assumptions which are often not valid for real data sets. Many physiological systems are highly nonlinear [11], so that linear analysis is inappropriate. Advanced data-mining methods, on the other hand, can be used to extract high-level information from complex biological systems without such troublesome pre-assumptions.

MA can be diagnosed by 24-h urine collection (gold standard). However, more convenient detection methods have been proposed in the literature [12]. The present study investigates whether it is possible to use advanced classification methods to indicate the occurrence of MA based *solely* on the routine screening in diabetic patients [13], without a separate urinary albumin concentration measurement test. Considering the rather high prevalence of chronic kidney disease in diabetic patients in Iran (14%–26%) [14], this will facilitate MA diagnosis, thus preventing later kidney complications. Moreover, this study could reveal which are the most significant factors for predicting MA, thus simplifying the diagnostic procedure.

The rest of the paper is organized as follows: in the next section, information about the subjects and the classification methods used in this study is presented. Section 3 provides the results of the classification methods and assesses their performance. Statistical feature selection is used to exclude irrelevant features. Finally, the conclusions are summarized in Section 4.

2. Materials and methods

2.1. Patients

Participants attended screening visits and a follow-up visit at the Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, where they underwent standardized interviews, physical assessment, and laboratory testing. We studied all the diabetic 2 patients who attended the above-mentioned center in 2012 whose clinical information was complete. The data were collected by trained technicians. The duration of diabetes was determined by subtracting the age at diabetes diagnosis from the current age. MA was defined as urinary albumin between 30 and 300 mg/day. Lipid profile (HDL, LDL, TG and CHOL) was measured after a 10- to 12-h fast. Our study was performed on 200 patients (130 males and 70 females) with type 2 (insulin-Independent) diabetes mellitus. All patients received conventional treatment. Also semiannual determinations of HbA1c, Bs2hpp, BP, BMI, and FBS values were recorded for participants. All subjects gave informed consent to the experimental procedure. The experimental protocol was approved by the Isfahan University of Medical Sciences Panel on Medical Human Subjects and conformed to the Declaration of Helsinki.

2.2. Statistical analysis

All statistical analyses and calculations were performed using the SPSS statistical package, version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive analyses were used to characterize the participants by socio-demographic and clinical factors. Continuous data were presented as mean $\pm$ SD and as proportions for categorical variables. Prevalence of MA was expressed as percentages. A two-sided P-value of <0.05 was considered statistically significant. Finally, classification was performed using Matlab and Statistics Toolbox Release 2011a (The MathWorks, Inc., Natick, Massachusetts, USA).

2.3. Classification methods

The following input features were used in this study: Age, Gender, BMI, DD, systolic BP, FBS, HbA1c, Bs2hpp, CHOL, LDL, HDL, and TG. BP was then converted to a nominal variable indicating the occurrence of hypertension. This was done because BP has been usually used to indicate hypertension as a risk factor in the literature. Two nominal variables (gender, BP) received special treatment when necessary. The outcome was classified as Normoalbuminuria (urinary albumin less than 30 mg/day) or MA (urinary albumin between 30 and 300 mg/day).

Machine learning methods applied to a variety of medical domains can be classified into the following major groups [15,16]: inductive learning of symbolic/qualitative rules (such as decision trees and neuro-fuzzy classifiers), statistical or pattern-recognition methods (discriminate analysis, Bayesian classifiers, support vector machines), and artificial neural networks. Among multivariate methods, linear and quadratic discriminant analysis (LDA and QDA), support vector machine (SVM), naïve Bayesian classifier (NBC), bagged decision trees (BDT), and adaptive neuro-fuzzy interference system (ANFIS) were chosen [16–18]. Also, we proposed an expert-based type-1 Mamdani fuzzy inference system, in which the rule fusion was performed using discrete particle swarm optimization (D-PSO). A statistical feature selection (FS) was also used to reduce the feature space. Its effect on the examined classifiers was studied. In the next section, the classification methods used in this study are introduced.

2.3.1. The proposed hybrid intelligent system (HIS)

Fuzzy classifiers (FCs) have been widely used in computer-aided diagnosis systems [19,20]. FCs assume an overlapping boundary between neighboring classes which is practical in many applications, providing a simple representation of the complex feature space.

Briefly, fuzzy *if-then* rules in a two-class classifier FIS are defined as follows:

$$\text{if } x_1 \text{ is } A_1^j \text{ and } x_2 \text{ is } A_2^j \text{ and } \ldots \text{ and } x_n \text{ is } A_n^j \text{ then } y \text{ is } \omega_i; \quad i=1,\ 2\ (w_j) \tag{1}$$

where, A_i^j and w_j are the ith input linguistic term and the weight (importance) of the rule index j ($j=1,\ldots, m$), and $[x_1,\ldots,x_n]$ is the feature vector (the clinical recordings for a subject) that is classified to class ω_i. Similarly, it is possible to change the rule consequent to a probability in which the input data belongs to one

of the underlying classes:

$$\text{if } x_1 \text{ is } A_1^j \text{ and } x_2 \text{ is } A_2^j \text{ and } \ldots \text{ and } x_n \text{ is } A_n^j \text{ then Prob}(\omega_1|y) \text{ is } B^j\ (w_j) \quad (2)$$

where, B^j is the output linguistic term of the rule index j ($j=1,\ldots, m$). Setting a probability threshold (e.g. 50%), it is possible to identify the output class as: class is ω_1 if the total output probability of the fuzzy system is not less than 50%. In our problem, ω_1 is the MA class. This structure is mostly suited with the Mamdani FIS, in which the output linguistic term is used instead of linear combination of rule antecedent. In the designed FIS, AND, and OR methods were the minimum and maximum. The implication and aggregation were the minimum and maximum, respectively. Finally, the centroid de-fuzzification was used as the output stage.

In the proposed FC, the membership functions of the input/output linguistic terms of all the parameters except gender and BP were initially designed by the experts. Since gender and BP are binary values, the unit step function was used as the corresponding MF. Spline-based Z-shaped and S-shaped were used for extreme low and high MFs and Gaussian was used elsewhere. The experts took into account the range of the normal/abnormal input parameters in the clinical literature and defined as many as input MF as necessary. For example, for the LDL, four MFs entitled as "Normal", "Borderline", "High" and "Very High" were designed. Also, three MFs "Normal", "Overweight" and "Obese" were designed for the BMI. Five levels of output probability "Low", "Medium Low", "Medium", "Medium High" and "High", were designed for the output linguistic terms. The outline of the MFs for the input/output parameters is shown in the "Figs. S1 and S2, Supplementary materials".

The other required parts of the FIS are the fuzzy rules. Choosing an appropriate number of rules is very important for the overall performance and generalization capability of a fuzzy system. There are different rule induction methodologies in the literature, mainly as systematic method [21], and heuristic approach [22–24]. The former category suffers from an exponential increase of number of rules (grid partitioning), the high impact of the clustering radius (subtractive clustering) and the problem of estimating the optimal number of clusters (FCM). These are the reasons that the optimal (compact) representation of the fuzzy rules is not feasible based on the first methodology. The latter category includes neural fuzzy and evolutionary fuzzy systems (such as evolutionary programming (EP), genetic algorithm (GA)) and swarm intelligence (ant-colony optimization (ACO), particle swarm optimization (PSO)). Using these heuristics, it is possible to find the optimal number of fuzzy rules and compact representation of the rule's antecedent. In the meanwhile, we used simultaneous rule learning to design our proposed FC approach, in which interaction of the fuzzy rules is required during their generation at the expense of increased computational complexity [22].

PSO, a promising new optimization technique, was used for inductive rule learning. Unlike evolutionary algorithms, the particle swarm does not use selection; the interactions of the whole population from the beginning result in iterative improvement [25]. PSO is a meta-heuristic population-based stochastic optimization algorithm, originally proposed to simulate the social behavior of a flock of birds [26]. PSO has been successfully applied to a wide range of optimization problems [27–29]. PSO is briefly discussed at the next section and is embedded into the FIS to find the optimum number and structure of the rules.

2.3.2. Particle swarm optimization (PSO)

In PSO, each "particle" is a candidate solution flying through the search space, whose position (x) and velocity (v) are iteratively updated in each dimension using the following formula [30]:

$$\begin{cases} v(t+1) = \omega v(t) + c_1 r_1 (p(t) - x(t)) + c_2 r_2 (g(t) - x(t)) \\ x(t+1) = x(t) + v(t+1); \quad v(1) \sim U(0,1) \end{cases} \quad (3)$$

where t is the time step (iteration number), $p(t)$ is the personal best solution of the particle, $g(t)$ is the best position found by the neighborhood of particle, with the coefficient ω being the inertia weight, c_1 and c_2 the cognitive and social acceleration coefficients respectively and finally r_1, $r_2 \sim U(0,1)$. In our work, the neighborhood of each particle was the entire swarm (star topology) [26]. The following modifications were made to the original PSO to ensure acceptable performance and avoid premature convergence:

- Velocity clamping was used to prevent explosion, thereby avoiding premature convergence [22]. Positions of the particles were also clamped to surf the finite search space.
- Randomized PSO (RPSO) was used to improve the chances of finding the global optimum [31]. Every 40 iterations, the positions of 40% of the particles were re-initialized.
- The inertia weight (ω), was initially set to 0.9 (at $t=1$), and was then linearly decreased to 0.5 (at $t=$max_iter) [32]. A large value of inertia weight favors global search ("exploration"), while a small value favors local search ("exploitation").
- Following the Multi-start PSO (MPSO) strategy [31], PSO was run five times. The global best particle found in each run was used as a candidate particle at the next run.

The other PSO parameters were set as follow: $c_1=c_2=1.49618$ [33], and max_iter=1000. The termination criterion was only based on the number of iterations.

2.3.3. Using PSO for inductive rule learning

The coding structure of a fuzzy rule is shown in Table 1. Each rule is represented by 12 discrete input MF index, a discrete output MF index, each of which has different range defined by the experts (Figs. S1 and S2, Supplementary material), a continuous fuzzy rule weight (importance) within [0,1], and finally a natural number with the value of 1 or 2, indicating the fuzzy operator for the rule's antecedent. Following the above rule coding, the interpretation of the rule code [−1, 0, 2, 3, 2, 0, 3, 0, 2, 1, 0, 0, 4, 0.75, 1] will be as follow:

IF the AGE is NOT "middle age", AND BMI is "overweight", AND DD is "very high", AND BP is "hypertension", AND HbA1c is

Table 1
The coding of a fuzzy rule based on the input and output MF index, the fuzzy weight and the fuzzy operator index including the range of the features.

Rule structure	Discrete MF index[a]													Continuous importance impact	Discreet antecedent index
	Age	Gender	BMI	DD	BP	FBS	HbA1c	CHOL	Bs2hpp	LDL	HDL	TG	ProbMA	Rule weight	Fuzzy operator[b]
Range	[−3,3]	[0,2]	[−3,3]	[−3,3]	[0,2]	[−3,3]	[−3,3]	[−3,3]	[−3,3]	[−4,4]	[−3,3]	[−4,4]	[1,5]	[0,1]	{1,2}

[a] The absolute values are the index of the MF (starting 1 for the leftmost MF; refer to supplementary material: part A for the structure of each input/output MF). The negative number implies the linguistic operator "not". The value of zero means that the corresponding feature does not exist in the rule. For the gender MF, "male" and "female" are represented by 1 and 2, respectively. The values of 1 and 2 for the BP MF, implies normal blood pressure and hypertension, respectively.

[b] The fuzzy operator for the rule's antecedent is "AND" and "OR" for the fuzzy operator values of 1 and 2, respectively.

"diabetes", AND Bs2hpp is "impaired glucose tolerance", AND LDL is "normal" THEN ProbMA is MH (Medium high); (rule weight=0.75).

The condition in which all of the input MF's code are 0 (no rule antecedent), was avoided. For more than one rule, their codes were concatenated in serial, to have the number of rules' parameters of 15*n_rule, where n_rule is the maximum number of possible rules. It was not necessary to run the algorithm for different rule number; instead the weight of the unnecessary rules will automatically tend to zero during the optimization procedure. The high number of rules will increase the complexity of the problem; thus increases the chance premature convergence, so n_rule parameter was initially set to 10. We have found that this number gives a good balance between under-fitting and over-fitting.

Accordingly, each particle had the dimension of (D=15*n_rule). The number of particles was (n_particles=round($10+2*D^{0.5}$)) [34]. The objective function was set to the accuracy of the FC on the whole training set. The initial rules of the PSO, for the first run, were defined by experts according to the qualitative rules taken from the literature. When the rule induction finished, the rules whose weights were less than 0.01, were excluded from the FIS rule list. The resulting FC is referred to as the "*hybrid intelligent system*" (HIS) throughout this manuscript. The Matlab code of the proposed PSO-based inductive rule learning system is available upon request.

2.3.4. Other tested classifiers

2.3.4.1. Linear and quadratic discriminant analysis (LDA, QDA). Discriminant analysis has been widely used in medical diagnostic systems [35]. LDA and QDA are two popular examples. In LDA, it is assumed that the patterns in each class are multivariate normally distributed with different means and identical covariance matrices. In QDA, the covariance matrices are assumed to be group-specific. LDA is robust against deviations from the multivariate normality assumption [36]. QDA is more flexible than LDA, because it has quadratic decision boundaries which produce elliptical, hyperbolic, parabolic or linear class boundaries; see [37] for details. Thus, a variety of patterns can be identified by QDA.

2.3.4.2. Support vector machine (SVM). The main concept of SVMs, which were originally developed for binary classification problems [38], is to use hyperplanes to separate data points of different classes[37]. In our study, the linear and radial basis function (RBF) kernels were used. The soft-margin parameter and the radius of the RBF kernel should be set properly, because inappropriate parameter settings end up with poor classification results. The method proposed by Wu and Wang [39] was used to set the tunable parameters. In the meanwhile, sequential minimal optimization (SMO) [40] was used to train the SVM classifier. SMO breaks the large QP SVM problem into a series of smallest possible QP problems, which are then solved analytically [40].

2.3.4.3. Naïve Bayesian classifier (NBC). Bayesian networks are examples of Bayesian statistical learning algorithms, and NBC is one of the simplest forms of these networks. Although it is simple and makes the (strong) assumption of class-conditional independence, NBC training is fast and it is tolerant to noisy and incomplete data [16]. NBC often performs quite well even if its assumption is violated. In our study, a Gaussian kernel function with an adaptive bandwidth parameter was used [41]. The Laplacian correction was used to avoid the case of probability values of zero.

2.3.4.4. Bagged decision trees (BDT). Decision trees (DT) have been widely used in medical (diagnosis) systems [42], since they are easy to understand and interpret,, allow the use of both continuous and nominal data,, are fast and are able to process large datasets [42]. However, it is difficult to design the optimal tree. The performance of the DT was improved by using a bagging (bootstrap aggregation for ensemble of DT) technique which involved combining the various outputs of learned DT on a bootstrapped training set into a single prediction [43]. The BDT returns the class that has been predicted most often (voting). In our study, BDT was implemented by a post-pruned ensemble of DT [43] using the *normalized gain ratio* criterion for feature selection in Quinlan's C4.5 DT induction algorithm [44]. Test set examples were then classified by a simple majority vote of the ensemble DT and ties were broken randomly.

2.3.4.5. Adaptive neuro-fuzzy interference system (ANFIS). ANFIS is an adaptive network that learns the rules and membership functions (MF's) from the data. It integrates the best features of fuzzy systems and neural networks [45]. The system learns the relationship between the inputs and output via a first-order Takagi Sugeno Kang (TSK) fuzzy inference system (FIS), where the fuzzy conclusion is the weighted linear combination of the inputs. Although the FIS output is usually continuous, it is possible to integrate it with the diagnosis systems via the *diagnosis likelihood ratio* [46]. In our study, the FIS output was set to the probability of having MA ranging from 0 to 1, and the cutoff value of 0.5 was used for MA diagnosis. The initial FIS was estimated using fuzzy C-means (FCM) from the input/output training data set. The number of clusters was estimated by the fuzzy extension of the silhouette criterion to eliminate the problem of unnecessary rules and tunable parameters [47]. The AND, and OR methods were the product and the probabilistic OR (algebraic sum). The implication and aggregation were the minimum and maximum, respectively. Finally, the de-fuzzification operator was weighted averaging.

2.4. Classifiers with statistical feature selection (FS)

In many classification problems, numerous candidate features are used for domain representation. Often many of these are irrelevant or redundant [48]. Thus, feature selection (FS) is used to detect relevant features leading to an increase in classifier accuracy.

To reduce the complexity of the examined classifiers as well as the proposed HIS system, multiple logistic regression (MLR), a statistical FS method, was used. Much has been written in the literature about the relative merits of MLR versus multiple linear regression [49,50]. MLR has been extensively used to identify relevant risk factors in epidemiological studies in which the outcome variable is categorical [51]. MLR, known as feature vector machine in machine learning, can be used to select statistically significant features [52–54]. After running MLR on the input features (excluding the intercept point in the analysis), the selected features were used in the tested classifiers. The resulting methods were called FS-LDA, etc.

2.5. Validation

The performance of the considered classifiers was assessed using the holdout method, an approach to out-of-sample evaluation, in which the dataset was split into two equal-size mutually

Table 2
The reported performance measures.

Sensitivity (Se)=TP/(TP+FN)	Specificity (Sp)=TN/(TN+FP)
Accuracy (Acc)=(TP+TN)/(TP+TN+FN+FP)	Precision (Pr)=TP/(TP+FP)
Recall (RL)=Power=Se	F_1-score=2 × Pr × RL/(Pr+RL)
False alarm=1-Sp=False positive rate=α (Type I error)	
β=1-Se=False negative rate (Type II error)	

exclusive sets (datasets 1 and 2). The classifiers were then trained on dataset 1 and tested on dataset 2 and vice versa [55,56]. Additionally, the repeated holdout estimate as well as 10-fold cross-validation were used to assess the performance of the best classifier in order to overcome a possible pessimistically biased error estimate [55]. The performance measures of the classifiers are listed in Table 2, along with their definitions. Of the measures, Sensitivity (Se), Specificity (Sp), Accuracy (Acc), and Precision (PR) are reported, while the other indices can be obtained as in Table 2. The performance indices taken into account cover most of the indices used in information theory and epidemiological studies [57,58]. Additionally, to determine whether one classifier outperformed another on the test set, McNemar's (Gillick) statistical test was used [55,59].

3. Results

The average age of the participants was 58 ± 9 years, with the average duration of diabetes being 10 ± 5 years. 65% were males. Fifty percent were hypertensive, and the prevalence of MA was 44%. The average BMI was 28.2 ± 4.3 kg/m^2, and 30% were obese. The socio-demographic and health characteristics of the participants, grouped by their classification as MA and Normoalbuminuria (NA), are depicted in Table 3.

The performance of the selected classifiers as assessed using the holdout method is shown in Table 4. Table 4 has two separate parts: the left part is related to the performance of the classifiers on dataset 2 after tuning (training) on dataset 1, while in the right part, classifiers were trained on dataset 2 and validated on dataset 1. The overall holdout accuracy is shown in the "OAcc" column of Table 4. Additionally, the results of McNemar's test for pairwise comparison of the different classifiers listed in Table 4 also shown (Table S1, Supplementary materials). "NBC" and "SVM-linear" outperformed the other classifiers except for "ANFIS" and "HIS". In other words, no classifiers outperformed "HIS" and "ANFIS" among the classifiers tested (Table S1).

Next, MLR was used for statistical feature extraction. The intercept point (bias) was not used in the model, and the significant features (p-value < 0.05) were selected. The features selected by MLR as being effective were "BMI", "AGE", "HbA1C" and "DD". The performance of the selected classifiers with feature selection (FS) is shown in Table 5 using the holdout method. Additionally, the results of McNemar's test for pairwise comparison of the different classifiers listed in Table 5 are also shown (Table S2, Supplementary materials). The overall accuracy of "FS-HIS" was 95%. "FS-HIS" outperformed the other classifiers while "FS-NBC" and "FS-SVM linear" received the 2nd and 3rd ranks (Table S2).

Four fuzzy rules inducted by PSO (when trained on dataset 1) in the FS-HIS method are shown in Table 6. The weights of the induced Fuzzy rules are also shown. Rule #4 was the most important rule ($w_4 = 0.92$) while the 3rd rule was the least important one ($w_3 = 0.04$). The value of the objective function (the accuracy of training on dataset 1) and the dataset 2 accuracy of the FS-HIS (when training on dataset 1) at some iterations (the 2nd PSO run), are shown in Fig. 1. The discrete nature of the improvement of the objective function was because of using 1the discrete-PSO algorithm. Additionally, the FIS system created by the FS-HIS (when trained on dataset 1) is shown (Fig. S3, Supplementary materials).

The performance of "FS-HIS" was further assessed using the repeated holdout ($N_r = 20$) and 10-fold cross-validation (Table 7). The average holdout accuracy "OAcc" for 20 repetitions and the average test-set accuracy indices (for 10 cross-checking repetitions) are shown (Table 7). In the worst case, the sensitivity and specificity of the FS-HIS were 94.7% and 85.1%, respectively. Moreover, the average accuracy obtained for repeated holdout and 10-fold cross-validation were 94.4% and 94.2%, respectively, showing that the accuracy of FS-HIS reported in Table 5 is not dependent on the *specific* training set/test set used in the algorithm. The high values of average precision (in addition to the low values of SD precision), reported in Table 7, revealed the *good* repeatability of the FS-HIS algorithm. Also, the inter-rater agreement between the gold

Table 3
Comparison of clinical and biochemical features of all the included subjects with normo- and microalbuminuria.[a]

Groups	**Normo**albuminuria ($n=113$)	**Micro**albuminuria ($n=87$)
Age (year)	65 ± 6 (51–58)	52 ± 6 (32–63)
Percentage women (%)	39	30
BMI (kg/m^2)	28.8 ± 4.8 (18.1–40.5)	27.5 ± 3.6 (20.3–39.8)
Hypertension (%)	53.6	46.4
Triglyceride (mmol/l)	158 ± 61 (48–332)	157 ± 73 (35–546)
HDL cholesterol (mmol/l)	52 ± 12 (27–76)	46 ± 10 (25–72)
LDL cholesterol (mmol/l)	108 ± 28 (41–194)	100 ± 22 (48–180)
Total cholesterol (mmol/l)	191 ± 34 (124–287)	178 ± 25 (108–263)
Fasting blood sugar (pmol/l)	145 ± 41 (75–273)	154 ± 6 (64–427)
HbA1C (%)	7 ± 1 (4.6 ± 11.4)	8 ± 2 (4.6–11.2)
Bs2hpp (mg/dl)	220 ± 61 (93–410)	235 ± 71 (80–446)
Diabetic duration (year)	10 ± 5 (5–25)	10 ± 4 (5–21)

[a] Values are mean ± S.D (range); BMI, body mass index; BP, blood pressure.

Table 4
The holdout performance estimate (%) of the selected classifiers.

Strategy	**Tuning on the dataset 1**								**Tuning on the dataset 2**								**OAcc**
Datasets	**Dataset 1**				**Dataset 2**				**Dataset 1**				**Dataset 2**				
Index classifier	**Se**	**Sp**	**Pr**	**Acc**	**Se**	**Sp**	**Pr**	**Acc**	**Se**	**Sp**	**Pr**	**Acc**	**Se**	**Sp**	**Pr**	**Acc**	
LDA	94	84	85	89	66	94	92	**80**	90	80	82	**85**	98	100	100	99	**83**
QDA	88	94	94	91	68	88	85	**78**	80	64	69	**72**	98	96	96	97	**75**
SVM Linear	94	84	85	89	68	96	94	**82**	92	80	82	**86**	100	100	100	100	**84**
SVM Rbf	100	100	100	100	74	80	79	**77**	100	42	63	**71**	100	100	100	100	**74**
NBC	94	90	90	92	76	92	90	**84**	90	82	83	**86**	98	100	100	99	**85**
BDT	82	100	100	91	80	100	100	**90**	40	84	71	**62**	62	96	94	79	**76**
ANFIS	98	94	94	96	68	96	94	**82**	82	74	76	**78**	98	100	100	99	**80**
HIS	80	76	77	78	82	72	75	**77**	84	90	89	**87**	80	96	95	88	**82**

Se: Sensitivity (%), Sp: Specificity (%), Pr: Precision (%), Acc: Accuracy (%), OAcc: The overall percentage accuracy (the average of the Acc of the classifier on the dataset 2 where it was tuned on the dataset 1 and vice versa); The classifiers: LDA and QDA (linear/quadratic discriminant analysis), SVM linear and Rbf (supported vector machines with linear/Rbf kernel), NBC (naïve Bayesian classifier with an adaptive Gaussian Kernel density estimator), BDT (bagged decision trees), ANFIS (adaptive neuro fuzzy inference system), and HIS (the proposed hybrid intelligent system).

Table 5
The holdout performance estimate (%) of the selected classifiers incorporating statistical feature selection (FS) based on multiple logistic regression (MLR).

Strategy	Tuning on the dataset 1								Tuning on the dataset 2								OAcc
Datasets	Dataset 1				Dataset 2				Dataset 1				Dataset 2				
Index classifier	Se	Sp	Pr	Acc	Se	Sp	Pr	Acc	Se	Sp	Pr	Acc	Se	Sp	Pr	Acc	
FS-LDA	92	82	84	87	62	96	94	**79**	94	88	89	**91**	98	100	100	99	**85**
FS-QDA	88	80	81	84	70	96	95	**83**	94	60	70	**77**	100	94	94	97	**80**
FS-SVM Linear	92	90	90	91	78	96	95	**87**	94	72	77	**83**	100	94	94	97	**85**
FS-SVM Rbf	96	96	96	96	70	94	92	**82**	92	62	71	**77**	100	100	100	100	**80**
FS-NBC	96	84	86	90	84	98	98	**91**	94	84	85	**89**	100	96	96	98	**90**
FS-BDT	96	86	87	91	100	94	94	**97**	34	76	59	**55**	60	76	71	68	**76**
FS-ANFIS	98	92	92	95	82	92	91	**87**	94	74	78	**84**	100	98	98	99	**86**
FS-HIS	94	90	90	92	100	96	96	**98**	94	90	90	**92**	100	100	100	100	**95**

Se: Sensitivity (%), Sp: Specificity (%), Pr: Precision (%), Acc: Accuracy (%), OAcc: The overall percentage accuracy (the average of the Acc of the classifier on the dataset 2 where it was tuned on the dataset 1 and vice versa); statistical feature selection (FS) was used prior to using the following classifiers: LDA and QDA (linear/quadratic discriminant analysis), SVM linear and Rbf (supported vector machines with linear/Rbf kernel), NBC (naïve Bayesian classifier with an adaptive Gaussian Kernel density estimator), BDT (bagged decision trees), ANFIS (adaptive neuro fuzzy inference system), and HIS (the proposed hybrid intelligent system).

Table 6
Fuzzy rules inducted by PSO in FS-HIS method.

Rule index	**Inducted rule**	**Rule weight**
1	If (AGE is Old) and (Hb1AC is Diabetes) then (ProbMA is Medium)	0.53529
2	If (AGE is Older) then (ProbMA is ML)	0.55594
3	If (BMI is Normal) or (AGE is Old) or (Hb1AC is Diabetes) or (DD is High) then (ProbMA is High)	0.040845
4	If (BMI is Normal) and (AGE is older) and (Hb1AC is Normal) and (DD is Medium) then (ProbMA is ML)	0.91870

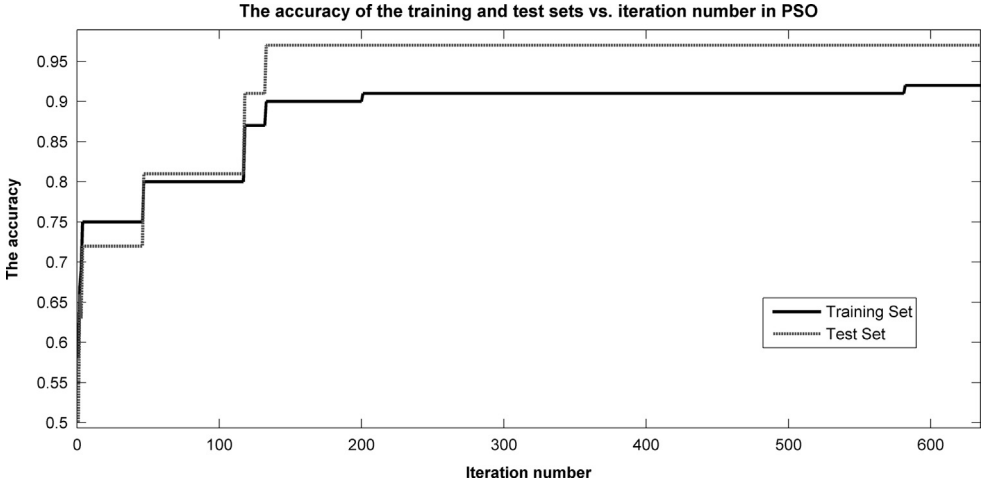

Fig. 1. The value of the objective function (the accuracy of the proposed classifier on the training set-solid line) and the accuracy on the test set (dotted line) in the second PSO run at some iteration.

standard and the results of FS-HIS was "almost perfect agreement" (min. Cohen's kappa coefficient = 0.91) [60].

4. Discussion

MA is a predictor of end-stage renal failure and death in patients with type 1 diabetes and a marker of increased mortality from cardiovascular disease for type 2 diabetes [5]. In population-based studies, the prevalence of microalbuminuria ranged from 12.3% to 27.2% and from 19.4% to 42.1% among those with type 1 and 2 diabetes, respectively [13]. Accordingly, it is recommended by the American diabetes association (ADA) that MA clinical tests must be scheduled annually for diabetic patients [61]. Additionally, the diabetes care schedule includes a HbA1C test every three months, and checking lipid profiles annually. By using the proposed MA classification system it will be possible to *accurately* identify the occurrence of MA based on "BMI", "AGE", "DD" and "HbA1C". Thus, MA screening can now be performed every three months when the HbA1C test is performed. This will make it possible to identify at-risk patients earlier and to send them for further clinical tests to prevent further MA damage.

According to the ADA, the gold standard for measuring urine albumin excretion (UAE) is a 24-h urine collection [62], as used in our study. However, a more convenient method to detect MA is the albumin (μg)/creatinine (mg) ratio (ACR) measured in a random urine specimen [63]. The ADA and the National Kidney Foundation (NKF) define microalbuminuria as an ACR between 30 and 300 μg/mg in both genders. However, it was shown that these cut-points are sex- and race-specific [62]. The sensitivity and specificity of the ACR were estimated as 73% and 96% in a recent study [12]. The sensitivity and specificity of the proposed FS-HIS

Table 7
The performance of the FS-HIS based on the repeated holdout ($N_r=20$) and 10-fold cross-validation (mean ± SD) [min,max].

Performance index test	Sensitivity	Specificity	Precision	Accuracy
Repeated holdout ($N_r=20$)[a]	99.2 ± 0.8 [98.2,100]	89.7 ± 2.1 [85.1,92.3]	90.6 ± 2.2 [83.9,93.0]	94.4 ± 1.2 [91.6,96.0]
10-Fold cross-validation[b]	98.7 ± 1.9 [94.7,100]	89.8 ± 2.6 [86.8,93.6]	90.2 ± 2.1 [86.1,92.7]	94.2 ± 1.0 [93.3,95.1]

[a] Each performance index was calculated as the average of the indices on the test set (when the classifier was tuned on the training set) and the indices on the training set (when the classifier was tuned on the test set). The training and test sets were randomly selected and the average of the performance indices were then reported over ($N_r=20$) repetitions.

[b] The database was randomly partitioned into 10 equal size subsamples. Of the 10 subsamples, a single subsample is retained as the test set, and the remaining 9 subsamples were used as training set. The cross-validation process is then repeated 10 times, with each of which was used exactly once as the test set. The average of the performance indices on resulting 10 test sets, were then reported.

method are estimated as 99% and 90% (Table 7), showing comparable results. Also, considering the maximum type I ($\alpha=0.10$) and II errors ($\beta=0.06$) of FS-HIS (Tables 2, 5 and 7), guarding against testing hypotheses suggested by the data (type III errors [64]) done by cross-validation (Table 7), and finally the "almost perfect agreement" between the gold standard and FS-HIS results in the worst case, the proposed method is promising for clinical diagnostic tests.

A meta-regression analysis of 22 studies ($>10{,}000$ cases) of diabetes has been recently performed [10]. The authors found out that FBS, HbA1C, BP, age, gender, DD, HDL and smoking are significant risk factors of MA. MLR revealed the effect of HbA1C, age, DD and BMI on MA in our study. Thus, there were disagreements on FBS, BP, gender, HDL and BMI. However, there have been several studies in the literature with controversial results on the above factors [5,10]. The difference could be due to two main limitations of our study: the relatively small sample size ($=200$ people), and the cross-sectional nature of our study. A larger sample size is needed for detailed investigations, and a cohort study is preferred to follow diabetes patients in a longitudinal study. The above limitations exit in several studies in the literature [10].

In our MA patients, BMI was correlated with BP. Also, BP was also correlated with age. Since MLR takes into account the intereffects between input parameters, this could be a possible explanation for why BMI was selected for our model while BP was not. HbA1C was *highly* correlated with FBS and Bs2hpp. Thus, HbA1C could predict FBS fluctuations, and was used in our model instead. HDL was correlated with age and TG (inversely). This might be a reason that age was selected in our model while HDL was not. Also, there existed correlations in our control subjects (Normoalbuminuria). For example, negative correlation between BP and BMI, *strong* correlation between HbA1C, FBS and Bs2hpp, and negative correlation between age and HDL. These correlations violated the class-conditional independence condition in NBC. However, this shows the robustness of the NBC algorithm since it had acceptable performance on the dataset (Tables 4 and 5). The normality condition was rejected for the age and DD variables. This could justify the marginal performance for QDA and the somewhat better performance for LDA; thus showing the robustness of LDA in comparison with QDA.

Statistical FS used in our study improved the performance of all of the classifiers tested (Tables 4 and 5). Instead of statistical FS, other methodologies such as optimal (e.g. branch and bound procedure), or sub-optimal searches (e.g. sequential forward/backward selection) could have been used [65]. Using these methodologies, different feature sets with acceptable accuracy and better physiological/clinical/practical interpretations could be introduced. For example, hypertension is the most significant contributing factor in the development of diabetic nephropathy (and is an MA risk factor) in type 2 diabetic patients [10,66]. BP has to be checked at every visit of a diabetic patient according to the diabetic care schedule recommended by the ADA [13]. On the other hand, calculation of DD requires accurate diabetes onset detection. Diabetes diagnostic criteria have been well defined [67–69]. However, no major organization recommends universal screening for diabetes. The World Health Organization (WHO) recommends only testing high-risk groups [70]. Thus, accurate onset detection of diabetes is not always feasible. Thus, it might be preferable to use hypertension instead of DD as a diagnostic criterion. It might be possible to use BP instead of DD, since DD was correlated with BP and BMI in the MA and control groups of our database. DD was also correlated with age in the MA group. A modified FS-HIS system using these criteria was trained using methods similar to those in Table 5. The resulting inducted fuzzy rules and the performance of this modified FS-HIS are listed (Table S3 and S4, Supplementary materials). The overall performance of this FIS system was 99%, which is quite promising.

FIS has provided a basis for representing imprecise knowledge and has formed a basis for human reasoning representation in medical applications [71]. A fuzzy classifier can be a convenient tool in the process of medical diagnosis [72]. An interpretable FIS solution is expressed in linguistic terms and should use few rules and original input variables [72]. The fuzzy rules inducted by PSO in the (modified) FS-HIS (Tables 6 and S3), are *more* interpretable than the accurate crisp classifiers used in our study. The (FS-) BDT classifier, on the other hand, is readable by clinicians because of the cut-off points, but it did not show acceptable performance (Tables 4 and 5). The interpretability of the FS-HIS could be improved by using Niching PSO [34], in which multiple global/local optima (sets of fuzzy rules) are located. Different sets of fuzzy rules, whose accuracies are acceptable, could be verified by clinicians to choose the most interpretable FIS. Also, the overall accuracy of FS-HIS, could be improved by further PSO-based tuning of the parameters of MF's used in the rules after fixing the fuzzy rule structures.

We proposed a new FS-HIS to identify MA without having to measure urinary albumin concentration. This method is accurate and precise and could be possibly used to identify MA in patients with type 2 diabetes. In the future, we will focus on the improvements of FS, fuzzy rule induction and clinical interpretation. A longitudinal MA database including more samples will be analyzed to increase the generalization capability of the developed HIS. Also, the prevalence of commonly examined demographics (gender and age) in a case/control groups will be considered to derive statements independent on the above-mentioned factors, if possible.

5. Summary

Microalbuminuria (MA) is an independent predictor of cardiovascular and renal disease in patients with type 2 diabetes. Detecting MA is an important screening tool to identify people with high risk of cardiovascular and kidney disease. The gold standard to detect MA is measuring 24-h urine albumin excretion. However, there exist more convenient, but less accurate, clinical tests such as random urine specimen albumin/creatinine ratio measurement. This manuscript presents a new method for MA diagnosis that uses clinical parameters usually monitored in type 2 diabetic patients without the need for additional measurements of urinary albumin. We designed an expert-based fuzzy MA classifier in which rule induction was performed by particle swarm optimization. A variety of other classifiers (linear and quadratic discriminate analysis, support vector machine, naïve Bayesian classifier, and adaptive neuro-fuzzy inference system) were also tested. Additionally, multiple logistic regression was used for statistical feature extraction,

improving the performance of all of the classifiers tested. The significant features were age, diabetic duration, body mass index and HbA1C (the average level of blood sugar over the previous 3 months, which is routinely checked every 3 months for diabetic patients). The resulting classifier was tested on a sample size of 200 patients with type 2 diabetes in a cross-sectional study. The performance of the proposed classifier was assessed using (repeated) holdout and 10-fold cross-validation. The minimum sensitivity, specificity, precision and accuracy of the proposed fuzzy classifier system with feature extraction were 95%, 85%, 84% and 92%, respectively. The proposed hybrid intelligent system outperformed other the tested classifiers and showed "almost perfect agreement" with the gold standard (min. Cohen's kappa coefficient = 0.91). This algorithm is a promising new tool for screening MA in type-2 diabetic patients. It provides a basis for representing imprecise knowledge and forms a basis for human reasoning representation. The proposed interpretable fuzzy classifier, expressed in linguistic terms, with few rules and input variables, can be a convenient tool in the process of MA diagnosis.

Conflict of interest statement

None declared.

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Appendix A. Supplementary material

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