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Original Article

Deep learning facilitates the diagnosis of adult asthma

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AHR, airway hyperresponsiveness;
AI, artificial intelligence; AUC, area under the ROC curve; BR, bronchodilator response; DNN, deep neural network; relu, Rectified Linear Unit; SVM, support vector machine; tanh, Tangent Hyperbolic Function

ABSTRACT

Background: We explored whether the use of deep learning to model combinations of symptom-physical signs and objective tests, such as lung function tests and the bronchial challenge test, would improve model performance in predicting the initial diagnosis of adult asthma when compared to the conventional machine learning diagnostic method.

Methods: The data were obtained from the clinical records on prospective study of 566 adult outpatients who visited Kindai University Hospital for the first time with complaints of non-specific respiratory symptoms. Asthma was comprehensively diagnosed by specialists based on symptom-physical signs and objective tests. Model performance metrics were compared to logistic analysis, support vector machine (SVM) learning, and the deep neural network (DNN) model.

Results: For the diagnosis of adult asthma based on symptom-physical signs alone, the accuracy of the DNN model was 0.68, whereas that for the SVM was 0.60 and for the logistic analysis was 0.65. When adult asthma was diagnosed based on symptom-physical signs, biochemical findings, lung function tests, and the bronchial challenge test, the accuracy of the DNN model increased to 0.98 and was significantly higher than the 0.82 accuracy of the SVM and the 0.94 accuracy of the logistic analysis.

Conclusions: DNN is able to better facilitate diagnosing adult asthma, compared with classical machine learnings, such as logistic analysis and SVM. The deep learning models based on symptom-physical signs and objective tests appear to improve the performance for diagnosing adult asthma.

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Introduction

Asthma, one of the most common diseases throughout the world, is defined clinically as the combination of variable respiratory symptoms and large changes in lung function. Diagnosis of this disease is based on international guidelines, including symptoms such as coughing, shortness of breath, and wheezing.^{1–3} As these symptoms are not specific to asthma, 30% of the asthma patients are misdiagnosed by a physician when the diagnosis was based on the symptoms alone.^{4–7} This misdiagnosis may lead to inappropriate treatment and then potentially physical and financial complications.⁸

There is no single reliable test ('gold standard') and there are no standardized diagnostic criteria for asthma. Thus, it is not possible to make an unequivocal evidence-based recommendation on how to make an asthma diagnosis.⁹ We previously demonstrated that symptom-sign score, which involved combining symptoms, including recurrent episodes and nocturnal worsening as well as physical findings, could determine the probability of asthma. However, if the diagnosis is considered as being of intermediate or low probability, further lung function tests, including obstructive spirometry and a positive bronchodilator test, could increase the probability of accurately diagnosing asthma.¹⁰ In that study, logistic analysis was used as a linear-regression model, and the accuracy of diagnosing asthma was limited to 70% on the determined symptom-sign score.

The experience of the physician in the diagnostic process is undeniable, and to avoid wasting time in the diagnosis, techniques based on artificial intelligence (AI) are being employed, so that the diagnosis is rapid, reliable, accurate, and

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knowledge-based.¹¹ One of the AI techniques used to solve real-world problems involves neural networks. Since the successful use of a deep learning neural network was demonstrated for an image classification task,¹² the deep learning technique has been gaining ground in medical image analysis. Deep neural network (DNN) has been developed for image analysis and has been used for deep learning as a non-linear regression analysis for classifying images.

The purpose of this study was to determine the efficacy of DNN for increased accuracy in the diagnosis of asthma and to make a comparison of the prediction performances of several deep learning methods, in particular logistic analysis and support vector machine (SVM). We also determined whether the objective test employing the typical symptoms of asthma was more useful for increased accuracy in diagnosing asthma.

Methods

Patients

Five hundred and sixty-six patients with nonspecific respiratory symptoms, who were reviewed in detail in prospective study of our previous paper,¹⁰ were enrolled in this study for re-analysis; 367 and 199 patients were diagnosed with asthma and non-asthma, respectively. There were 345 women and 221 men with a median age of 52 (18–88) years. The diagnosis of asthma was based on a relevant symptom history, and then established by a positive finding for reversibility with a bronchodilator response (BR) and/or a positive test for airway hyperresponsiveness (AHR). And then, physicians with expertise in asthma diagnosis made the final diagnosis as asthma. A positive methacholine-induced AHR test defines 8 mg/mL as below the provocative concentration causing a 20% fall in the FEV1 (PC20). The study was approved by our institutional ethics committee, and all subjects provided informed consent.

Preparation for three classifiers

We assessed the accuracy for diagnosing asthma using three classifiers: logistic analysis, SVM, and DNN. The Keras code^{13,14} combined with Google's TensorFlow^{15,16} was used. On TensorFlow's processing to explicitly initialize the variables, the input was to weigh normalization with data-dependent initialization. Additionally, to achieve a better integration with SVM, we used the scikit-learn. Randomly, 80% of the data were classified as training data, and the remaining 20% as testing data for each proposed system. Machine learning techniques have tuning parameters, such as the number of neurons in deep learning, batch size, epochs, dropout, and activation functions, those are also called the hyper-parameters.¹⁷ Since using all of the data samples to tune hyper-parameters may cause over-fitting, training data are used for tuning hyper-parameters. For automatic model tuning of learning hyper-parameters, a library of Talos package was used. The Jupyter Notebook (IPython Notebook) was used in order to share documents that contained live code: equations, visualizations, and narrative text.

Logistic regression analysis

For the logistic analysis, the network layers were implemented as input, hidden, and output layer. The input layer is linear and is only responsible for data transferring from the internal structure of the network. One hidden layer and the outlet layers are the sigmoid type and perform calculations on the network.

Support vector machine (SVM)

The support vector machine (SVM) model was used. For binary classification SVM, LIBSVM¹⁸ from the scikit-learn library with either the linear or Radial Basis Function (RBF) kernel was used. Other feature extraction or feature quantity selection was not performed so that we matched the criteria of the input data used in the deep learning training.

Deep neural network (DNN)

We implemented a deep learning model that uses the DNN shown in Figure 1 for use in our classification system. The DNN is a feed-forward neural network composed of more than one hidden nonlinear layer. It is characterized by a set of weight matrices, bias vectors, and a nonlinear activation function.

Statistics

Finally, a computer program consisting of three different classifiers, logistic regression, and SVM, was developed, trained to categorize any given new questionnaire, and suggest a diagnosis. For estimating the diagnostic accuracy, we applied a ten-fold stratified cross validation. The test dataset was used to calculate the ROC curve and the area under the ROC curve (AUC),¹⁹ based on a Keras framework in Python (Python 3.6.1, Python Software Foundation, Wilmington, DE, USA). The AUC is a commonly used criterion for assessing computational target prediction methods.^{20,21} To assess the AUC differences between classification models, we used either the paired or unpaired version of DeLong's test for ROC curves, as appropriate.²² All *P* values were assessed at an alpha of 0.05. Statistical analysis was performed using the R version 3.4 with both the pROC package and scikit-learn 0.18.1.^{23,24}

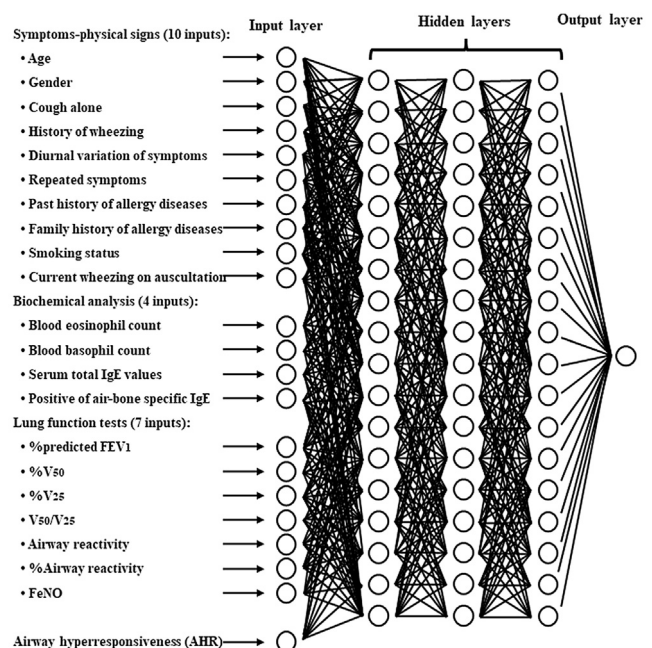


Fig. 1. Structure of deep neural network (DNN) with input, hidden layers, and output layers. For tuning the hyper-parameter, the network structure is designed as 22-18-18-1 in which there are 22 nodes in the input layer, 18 nodes in the hidden layer, followed with two-times repeated hidden layers, and then 1 node in the output layer (asthma; yes = 1, no = 0). In the process of propagation, "relu" was chosen as the activation function. We trained with batches of 50 samples using the Adam optimizer for the back propagation learning technique, limiting our training to 300 epochs.

Results

Patients and input data

Among the total of 566 recorded cases evaluated, 367 patients suffered from asthma and 199 cases did not have this disease. In the records of the asthmatic patients, 22 inputs were recorded in relation to the diagnosis as below:

- (1) Symptom-physical signs (10 inputs): age which was an actual variable, sex which was a dichotomous variable (female = 0, male = 1), cough, history of wheezing, diurnal variation of symptoms, repeated symptoms, past history of allergy diseases, family history of allergy diseases, smoking history, and current wheezing on auscultation which were as dichotomous variables (yes = 0, no = 1),
- (2) biochemical findings (4 inputs): number of peripheral eosinophils, number of peripheral basophils, total IgE values which were actual variables, and a positive of air-bone specific IgE which was a dichotomous variable (yes = 0, no = 1),
- (3) lung function tests (7 inputs): %predicted FEV1, air flow rate at 50% vital capacity (V50), air flow rate at 25% vital capacity (V25), V50/V25, increase volume in FEV1 after bronchodilator, percent increase volume in FEV1 after bronchodilator, and FeNO which were actual variables, and,
- (4) bronchial challenge test using methacholine provocation (1 input): AHR which was a dichotomous variable (yes = 0, no = 1).

Logistic regression analysis

Logistic regression analysis is one of the machine learning algorithms for binary classification. Logistic analysis is a type of supervised learning, which groups the dataset into classes by estimating the probabilities using a logistic/sigmoid function. Logistic analysis is constructed as a simple neural network with one layer. The accuracy of diagnosing adult asthma based on combined factors with symptom-physical and biochemical factors, on combined factors with symptom-physical signs, on biochemical and lung function factors, and on the full set of factors was 65%, 68%, 82%, and 94%, respectively (Fig. 2). The ROC curve is shown in Figure 3 with a model trained on all 22 inputs that yielded an AUC of 0.97.

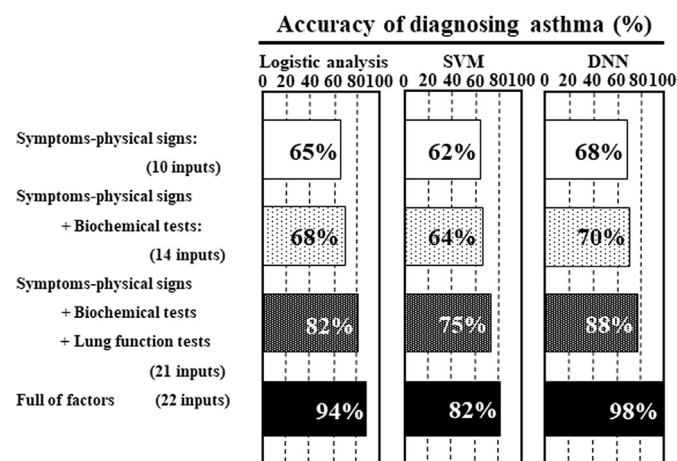
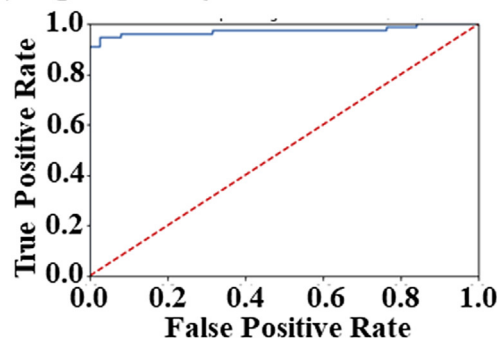
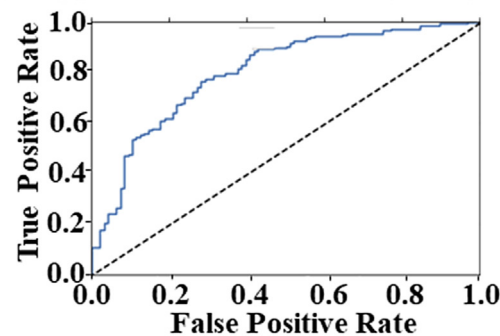


Fig. 2. Accuracy of diagnosing asthma with 3 different classifiers: logistic analysis, support vector machine (SVM), and deep neural network (DNN).

(A) logistic analysis



(B) support vector machine (SVM)



(C) deep neural network (DNN)

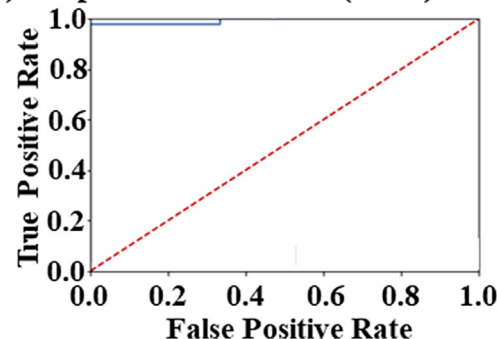


Fig. 3. Receiver operating characteristic (ROC) in 3 different classifiers: (A) logistic analysis, (B) support vector machine (SVM), and (C) deep neural network (DNN).

Support vector machine (SVM)

For analyzing SVM, the respective cost parameter (C: 1 or 10) and the kernel parameter (linear or rbf: $\gamma = 0.1, 0.01, 0.001$) were used depending on the number of factors, which were the results of the hyper-parameter optimization with the keras mold by talos (i.e. kernel = 'linear', 'rbf': C = 1, 10, 100, 1,000, and gamma = 0.000001, 0.00001, 0.0001, 0.001, 0.01) (Table 1). Scoring for the grid search was performed on the basis of the mean AUC-receiver operating characteristic obtained by 10-fold cross validation of the grading data. The data set used in both the training and validation was the same as that used in the deep learning model. Models trained on 10 inputs, composed of symptom-physical signs, yielded an accuracy of 62% (Fig. 2). Models trained on 14 factors, composed of symptom-physical signs and biochemical analysis, yielded an accuracy of 64%. Models trained on combined 21 inputs yielded an accuracy of 75%. Models trained on the full set of factors, including AHR, yielded an accuracy of 82% and an AUC of 0.83 (Fig. 3).

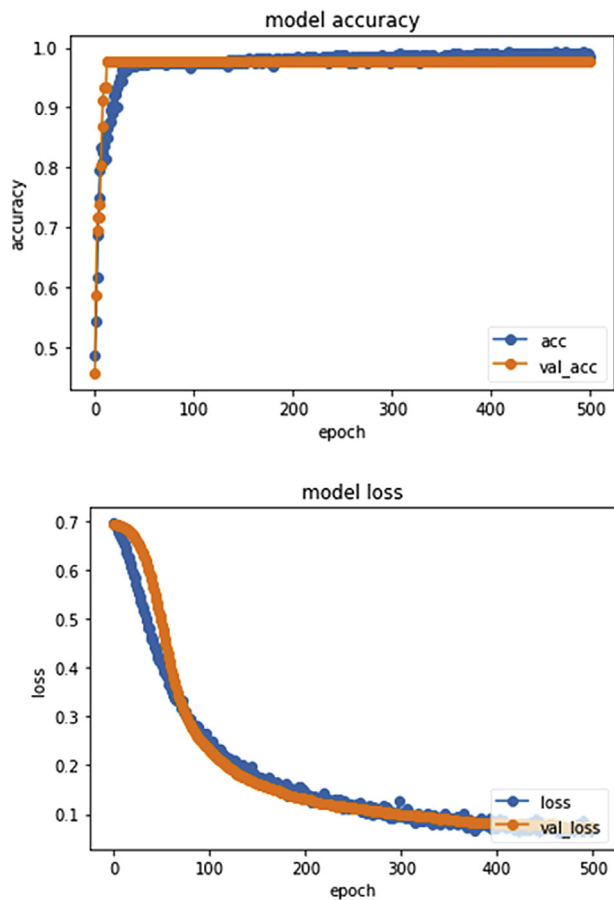


Fig. 4. Plots of deep neural network (DNN) accuracy and loss history error on training set size (epoch). Model accuracy and loss on both the training and validation sets continue to increase and decrease, respectively, to a plateau during training set size (epoch), when 22 full sets of factors were inputted. Our model is judged as no-overfitting.

Table 1

Area under the curve (AUC) and hyper-parameters for diagnosing asthma using the support vector machine (SVM) technique.

	AUC	Hyper-parameter
Symptom-physical signs [†] (10 inputs)	54.5 ± 0.8	kernel: 'rbf', C: 10, gamma: 0.1
Symptom-physical signs [†] and biochemical tests [‡] (14 inputs)	57.6 ± 0.1	kernel: 'linear', C: 1, gamma: 0.001
Symptom-physical signs [†] , biochemical tests [‡] and lung function tests [§] (21 inputs)	64.5 ± 0.1	kernel: 'rbf', C: 1, gamma: 0.01
All factors [§] (22 inputs)	83.0 ± 0.1	kernel: 'rbf', C: 10, gamma: 0.01

[†] Ten symptom-physical signs are included: age, sex, history of wheezing, diurnal variation of symptom, recurrent episodes, medical history of allergic diseases, family history of allergic disease, and wheeze sound.

[‡] Four biochemical tests are included: serum total IgE, specific IgE to air-borne allergen (≥ 0.35 kU/l), serum eosinophil counts, and serum basophil counts.

[§] Seven lung function tests are included: FEV₁ reversibility of FEV₁ after inhaled procaterol, and FeNO.

[¶] All factors are included: symptom-physical signs (10 factors), biochemical tests (4 factors), lung function tests (7 factors), and bronchial reactivity for the methacholine challenge test.

Deep neural network (DNN)

A hyper-parameter optimization selects which parameter is the best way for learning for activation of function, network structure, number of batch sizes, and number of epochs. The activation

function for activating the network in the forward propagation is the Rectified Linear Unit (relu) or the Tangent Hyperbolic Function (tanh) for the hidden layer and the sigmoid type for the outlet layers. The network structure was designed according to appropriate hyper-parameters (Table 2). One example of the network structure, when all of the factors were inputted, is shown in Figure 1. The architecture was 22-18-18-18-1 in which there are 22 nodes in the input layer, 18 nodes in the hidden layer, followed two-times repeated hidden layer, and then 1 node in the output layer (asthma: yes = 1, no = 0). In the process of propagation, "relu" was chosen as the activation function for the tuning hyper-parameter. We trained in batches of 50 samples using the Adam optimizer for the back propagation learning technique,²⁵ limiting our training to 300 epochs. Figure 4 shows the accuracy and loss rates on training and the validated progresses. When 2 progresses converged, there was no-over-fitting in our model.

Models trained on 10 inputs of symptom-physical signs yielded an accuracy of 68%. Models trained on combined factors with symptom-physical signs and biochemical factors yielded an accuracy of 70%. Models trained on combined factors with symptom-physical signs, biochemical factors, and lung function factors yielded an accuracy of 88%. Models trained on the full set of factors achieved an accuracy of 98% and an AUC of 0.99 (Fig. 3).

Comparisons of AUC among three classifiers

In order to assess AUC differences between classification models, DeLong's test for ROC curves demonstrated a significant difference between DNN and SVM ($P = 0.01$), as well as between DNN and logistic analysis ($P = 0.01$).

Discussion

The aim of this study was to develop an intelligent system for diagnosing the presence or absence of asthma in which the clinical features in terms of influencing the output were investigated. As a result, we used deep neural networks for diagnosing adult asthma and reached 98% accuracy if the input contained the complete set of patient information.

Computer-aided diagnosis (CAD) is a useful approach to improve diagnostic accuracy, and involves combining information provided by experts with machine learning methods. Machine learning can robustly diagnose adult asthma using complete clinical information. Zonnour and colleagues reported that a computerized intelligent system for detecting asthma in children known as the fuzzy intelligent system designed to predict asthma, was 100% correct.²⁶ Another study compared statistical methods for prediction accuracy of asthma persistence in children and found that Bayesian analysis exhibited high accuracy (approximately 86%) when compared with Artificial Neural Networks (ANN) (approximately 81%), which is one of the statistical and artificial intelligence techniques.²⁷ ANN have the potential to become a more widely used classification algorithm, but it is less commonly used because of the time-consuming parameter tuning procedure, the numerous types of neural network architectures to choose from, and the high number of algorithms used for training ANN. In this study, we determined that DNN is a useful tool for diagnosing adult asthma.

Models using neural networks frequently have difficulty analyzing systems with a large number of inputs due to the longer time required to train the system and the possibility of over-fitting the model during the training time.²⁸ In this study, hyper-parameters were tuned in order to avoid the over-fitting, and then convergence of training and validated progress could be confirmed on both the accuracy and loss rates (Fig. 4).

Table 2

Area under the curve (AUC) and hyper-parameters for diagnosing asthma using the deep neural network (DNN) technique.

	DNN	Hyper-parameter
Symptom-physical signs [†] (10 inputs)	63.2 ± 0.2	activation function: relu, hidden neuron: 22, hidden layer: 3, epochs: 300, batch size: 58, dropout: 0
Symptom-physical signs [†] and biochemical tests [‡] (14 inputs)	69.7 ± 0.4	activation function: relu, hidden neuron: 11, hidden layer: 2, epochs: 150, batch size: 56, dropout: 0
Symptom-physical signs [†] , biochemical tests [‡] and lung function tests [§] (21 inputs)	83.2 ± 0.2	activation function: tanh, hidden neuron: 22, hidden layer: 3, epochs: 150, batch size: 58, dropout: 0
All factors [¶] (22 inputs)	98.7 ± 0.1	activation function: relu, hidden neuron: 18, hidden layer: 3, epochs: 300, batch size: 50, dropout: 0

[†] Ten symptom-physical signs are included: age, sex, history of wheezing, diurnal variation of symptom, recurrent episodes, medical history of allergic diseases, family history of allergic disease, and wheeze sound.

[‡] Four biochemical tests are included: serum total IgE, specific IgE to air-borne allergen (≥ 0.35 kU/l), serum eosinophil counts, and serum basophil counts.

[§] Seven lung function tests are included; FEV₁, reversibility of FEV₁ after inhaled procaterol, and FeNO.

[¶] All factors include symptom-physical signs (10 factors), biochemical tests (4 factors), lung function tests (7 factors), and bronchial reactivity for the methacholine challenge test.

Table 3

Area under the curve (AUC) for diagnosing asthma using three classifiers: logistic regression, support vector machine (SVM), and deep neural network (DNN).

	Logistic regression	SVM	DNN
Symptom-physical signs [†] (10 inputs)	72.6 ± 1.4	54.5 ± 0.8	63.2 ± 0.2
Symptom-physical signs [†] and biochemical tests [‡] (14 inputs)	84.2 ± 0.9	57.6 ± 0.1	69.7 ± 0.4
Symptom-physical signs [†] , biochemical tests [‡] and lung function tests [§] (21 inputs)	88.2 ± 0.9	64.5 ± 0.1	83.2 ± 0.2
All factors [¶] (22 inputs)	98.3 ± 0.8	83.0 ± 0.1	96.8 ± 0.1

[†] Ten factors of symptom-signs are included: age, sex, history of wheezing, diurnal variation of symptom, recurrent episodes, medical history of allergic diseases, family history of allergic disease, and wheeze sound.

[‡] Four biochemical tests are included: serum total IgE, specific IgE to air-borne allergen (≥ 0.35 kU/l), serum eosinophil counts, and serum basophil counts.

[§] Seven lung function tests are included: forced expiratory volume in one second FEV₁, reversibility of FEV₁ after inhaled procaterol, and FeNO.

[¶] All factors are included: symptom-physical signs (10 factors), biochemical test (4 factors), lung function tests (7 factors), and bronchial reactivity for the methacholine challenge test.

When comparing the accuracy of diagnosing adult asthma among the three classifiers, we found that the best classification results were obtained by DNN with a 98% overall accuracy. The application of deep learning techniques currently has a very large advantage over SVM approaches in both accuracy and data handling. SVM approaches are an extremely popular and well-researched class of supervised learning models that do not use the computational power of deep learning.²⁹ While comparing the classification techniques, we observed variable results depending on the method used. The accuracy differs between SVM and DNN (Table 3), when analyzing the same set of data. DNN is able to classify the data with more accuracy as compared to that of SVM. Our results showed that our logistic analysis model achieved a high accuracy in diagnosing adult asthma. The reason might be that the logistic analysis model that we used is a simple neural network without a hidden layer and with supervised machine learning.

One of the most important factors in the development of the DNN is to select the appropriate structure and to use optimal data input. We used a DNN algorithm with tuning hyper-parameters. We tuned the model architecture using a hyper-parameter. We tested our task classifier performance with the ten-fold cross-validation approach. The evaluation results showed that the precision and recall values of our classifier were very high. By selecting the optimum data as input to the network using statistical methods, the amount of data that has the most efficiency in outlets can be selected. Our result is in concordance with some previous reports,^{4–7} that found 30% of the patients diagnosed with asthma by a physician were misdiagnosed when objective tests were not used. In contrast, we found that the DNN model was approximately 70% accurate for diagnosing adult asthma, based on symptom-physical signs as input data. Then, we assessed the accuracy of diagnosing adult asthma with different additional factors as input data. Additional data, including lung function tests and AHR each

resulted in an additional 10% increment for the accuracy of diagnosing asthma.

There is a limitation in our study. Depending on the specific situation and certain circumstances, it might be possible to prove that one of the techniques is superior over the others, which might fit the situation more accurately than the other techniques. In some situations, SVM was superior to the deep learning algorithm in terms of accuracy of classification.³⁰

This study seems to be the first paper that computers had almost comparable performance to specialist on the diagnosis of adult asthma. DNN is able to accurately predict disease based on all clinical findings in 98% of the cases. Our simple approach using DNN is more accurate than conventional machine learning methods and can be employed to implement practical personal assistant services. More information is required to obtain more accuracy. This action will lead to an appropriate education of the network and will increase the accuracy of its decision making. The next step was to persuade more hospitals to use the technology and investigate transferring the AI-based to primary care.

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Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

KT, HS and YT had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. KT, HT, TI, HS, AY, and YT contributed substantially to the study design and interpretation. KT and RN contributed to data analysis and the writing of the manuscript.

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