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Prediction of ischemic heart disease in patients with diabetes mellitus: Machine learning study on population data

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ABSTRACT

Objective: The main symptom of ischemic heart disease (IHD) is chest pain and diabetic patients are likely to not perceive chest pain due to neuropathy. Therefore, the prediction of IHD in patients with diabetes mellitus is crucial. In this study, we aimed to predict IHD in patients with diabetes mellitus using various machine learning techniques. Additionally, we aimed to interpret the machine learning model.

Materials and Methods: We used eXtreme Gradient Boosting (XGBoost), logistic regression, Multi-Layer Perceptron (MLP), random forest, decision tree and K-Nearest Neighbors (KNN) algorithms to predict IHD in patients with diabetes mellitus. Additionally, we used the SHapley Additive exPlanations (SHAP) method to interpret our machine learning model.

Results: According to performance analysis, the XGBoost model had a superior performance with 0.814 area under the curve (AUC) on the training set and 0.795 AUC on the test set. The Brier score of the XGBoost model was 0.153. SHAP analysis results showed that the presence of hypertension has the highest contribution to the presence of IHD in patients with diabetes mellitus.

Conclusion: Machine learning has the potential to provide decision support to clinicians in the identification of IHD in patients with diabetes mellitus.

Keywords: Ischemic heart disease, Diabetes mellitus, Machine learning, Explainable artificial intelligence

1. INTRODUCTION

Diabetes mellitus refers to the chronic dysfunction of insulin-producing cells and it is responsible for high morbidity and mortality worldwide [1, 2]. In 2021, 536.6 million people were affected by diabetes mellitus and in 2045, it is expected to affect 783.2 million people [3]. Furthermore, cardiovascular diseases are the most frequent cause of mortality [4]. Within cardiovascular diseases, ischemic heart disease (IHD) is the most frequent disease and the main reason for global mortality [4, 5]. In the future, the prevalence of IHD is expected to increase owing to population aging and economic inequalities [6, 7].

The risk of cardiovascular disease is doubled in patients with diabetes mellitus and IHD is the main cause of mortality among diabetes mellitus patients [8]. The most common symptom or indicator of IHD is chest pain [9]. However, diabetic patients tend to have neuropathy, which damages their sensory functions [10]. As a result, diabetic patients with IHD are likely to not perceive and experience chest pain [11, 12]. This situation may lead to delayed diagnosis and treatment. Therefore, the prediction of IHD in patients with diabetes mellitus is crucial. Machine learning techniques can be used to develop predictive models that support early detection of IHD in the diabetic population.

Several studies have used machine learning for predicting cardiovascular outcomes in diabetic patients. These studies mainly focused on coronary heart disease [13, 14] or cardiovascular disease [15-17] rather than IHD specifically. Most of these studies have been conducted on patients with type 2 diabetes mellitus [13, 15, 16], often excluding type 1 diabetes mellitus despite its significant relationship with cardiovascular diseases [18]. Additionally, these studies used hospital-based [13, 14, 16, 17] or insurance-based [15] datasets rather than population-level data, which would be more beneficial for developing more generalizable models. Addressing these gaps could provide a more comprehensive understanding of IHD risk in diabetes mellitus patients and improve early prediction strategies.

In this study, our primary objective was to develop a machine learning model to predict IHD in patients with diabetes mellitus using various machine learning techniques. Additionally, we aimed to interpret our prediction model by using SHapley Additive exPlanations (SHAP) analysis.

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2. MATERIALS and METHODS

Dataset

In the present study, a publicly available dataset was used which contains electronic medical records (EMR) of patients who were diagnosed with diabetes mellitus in Istanbul, Turkey [19]. The ethical approval for this study was obtained from Akdeniz University, School of Medicine, Clinical Scientific Research Ethics Committee (date: 31.10.2024, approval number: TBAEK-698). The original dataset consisted of 106 variables including demographics, laboratory tests, comorbidities, and prescription records of patients. During data curation, noise, extreme, irrational, and missing values were checked and excluded from the dataset. The original dataset did not contain any missing values. Further details about data curation can be found in the reference [19].

Data preprocessing

From the original dataset, categorical variables with highly imbalanced distributions were excluded. To assess multicollinearity, Variance Inflation Factors (VIFs) were used with a 2.5 cut-off value [20]. Variables exceeding the VIF threshold were removed. As a result, 78 variables were used to predict IHD in patients with diabetes mellitus. The list of all input variables is presented in the Supplementary Document.

The original dataset included the EMR of 77,724 patients. To divide the dataset into training and test sets, a 70:30 ratio was used. During the training and test split, the dataset was stratified by output variable to maintain the same distribution of outcomes in both the training and test sets. As a result, in the training dataset, 14,652 (26.9%) patients were diagnosed with IHD, and 39,754 (73.1%) patients were not. Similarly, in the test dataset, 6,280 (26.9%) patients were diagnosed with IHD, and 17,038 (73.1%) patients were not. After dividing the dataset into training and test sets, numerical variables were standardized over the training data using the StandardScaler function from the scikit-learn library in Python (version 3.9.7).

Machine learning model development

The training set (n=54,406) was used in the development of the machine learning models. Six machine learning algorithms were employed for modeling, briefly described below.

eXtreme Gradient Boosting (XGBoost) is an ensemble learning method that combines various weak learners to create a strong learner and offers the following advantages: it minimizes computation time, avoids overfitting, and effectively handles missing values [21, 22]. **Random forest** is another ensemble method that creates multiple uncorrelated decision trees and aggregates their predictions to achieve more accurate results [23]. It is widely used in medicine due to its ability to handle complex and nonlinear relationships [24]. **Logistic regression** is a statistical method used for classification that estimates the probability of a binary outcome [25]. Additionally, it can determine the relationship between the dependent variable and independent features [26]. **Multi-Layer Perceptron (MLP)** is a widely used neural network approach that comprises an input layer, hidden layers, and an output layer, with each layer containing neurons [27]. **Decision tree** use a rule set to make predictions with a structure like a tree [28]. It has been applied to a variety of clinical problems, especially for classification tasks [29]. Lastly**, K-Nearest Neighbors (KNN)** identifies the K nearest neighbors and assigns the outcome based on the nearest neighbors [30].

Random search hyperparameter optimization was performed using 10-fold cross-validation to optimize the hyperparameters of the models. The selected hyperparameters for each machine learning model are presented in Table I. Python (version 3.9.7) was used for modeling.

Table I. *The selected hyperparameters for each machine learning model*

Model	Hyperparameters
XGBoost	*colsample bytree = 0.79, gamma = 0.75, learning rate = 0.08, maximum depth = 5, minimum child weight = 9, subsample = 0.54*
Logistic Regression	*C = 0.09, penalty = l1, solver = saga*
MLP	*activation = logistic, alpha = 0.01, hidden layer sizes = (51,), learning rate init = 0.05, max_iter = 500, solver = adam*
Random Forest	*criterion = gini, maximum depth = 6, maximum feature = sqrt, minimum samples split = 0.03, number of estimators = 219*
Decision Tree	*criterion = entropy, maximum depth = 8, maximum features = None, minimum samples split = 0.03*
KNN	*number of neighbors = 49*

MLP: Multi-Layer Perceptron, KNN: K-Nearest Neighbours, XGBoost: eXtreme Gradient Boosting

Evaluation

The performance of the machine learning models was evaluated using area under the curve (AUC), precision-recall AUC (PR AUC), Matthews correlation coefficient (MCC), kappa statistics, accuracy, precision, recall, and f1-score, with 95% confidence intervals (CIs) calculated for each metric on both training (n=54,406) and test (n=23,318) sets. To assess the optimal cut-off value for each prediction model, Youden's index was used. The calibration plot and Brier score were used to test the agreement between the probabilities predicted by models and observed outcomes [31] of the best-performing model. Python (version 3.9.7) was used to evaluate machine learning models.

Model Interpretation

The best-performing model was interpreted using SHAP analysis. Python (version 3.9.7) was used for SHAP analysis.

Statistical Analysis

Categorical features were summarized as number and percentage, numerical features were summarized as median (Q1-Q3, 25th-75th percentile) or mean ± standard deviation. The normal distribution of the numerical data was analyzed using Q-Q plots. Differences between categorical variables

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were analyzed using Chi-square test. Due to the violation of the normality assumption, Mann-Whitney U test was used to compare independent groups. Jamovi v2.2.5 was used for statistical analysis.

3. RESULTS

Dataset Characteristics

The descriptive statistics of the dataset are shown in Supplementary Document.

Model Evaluation

The performance analysis of the machine learning models for the prediction of IHD in patients with diabetes mellitus is shown in Table II. Additionally, the receiver operating characteristic (ROC) curves of the prediction models are presented in Figure 1, and PR curves of the prediction models are presented in Figure 2. XGBoost achieved the highest AUC, with 0.814 (95% CI: 0.810–0.818) on the training set and 0.795 (95% CI: 0.788–0.801) on the test set. Logistic regression was the second best-performing model, with an AUC of 0.796 (95% CI: 0.792 – 0.800) on the training set and 0.794 (95% CI: 0.788 – 0.800) on the test set. MLP and random forest showed similar performance, with AUCs of 0.789 and 0.786, respectively, on the test set. Decision tree model had lower performance, with an AUC of 0.787 (95% CI: 0.783 – 0.791) on the training set and 0.778 (95% CI: 0.771 – 0.785) on the test set. KNN had the lowest AUC, with 0.781 (95% CI: 0.776 – 0.785) on the training set and 0.749 (95% CI: 0.742 – 0.756) on the test set. According to the performance analysis, the XGBoost model had the highest AUC and was selected as the representative model for further analysis.

The calibration plot of the XGBoost model is presented in Figure 3. The Brier score of the XGBoost model was 0.153.

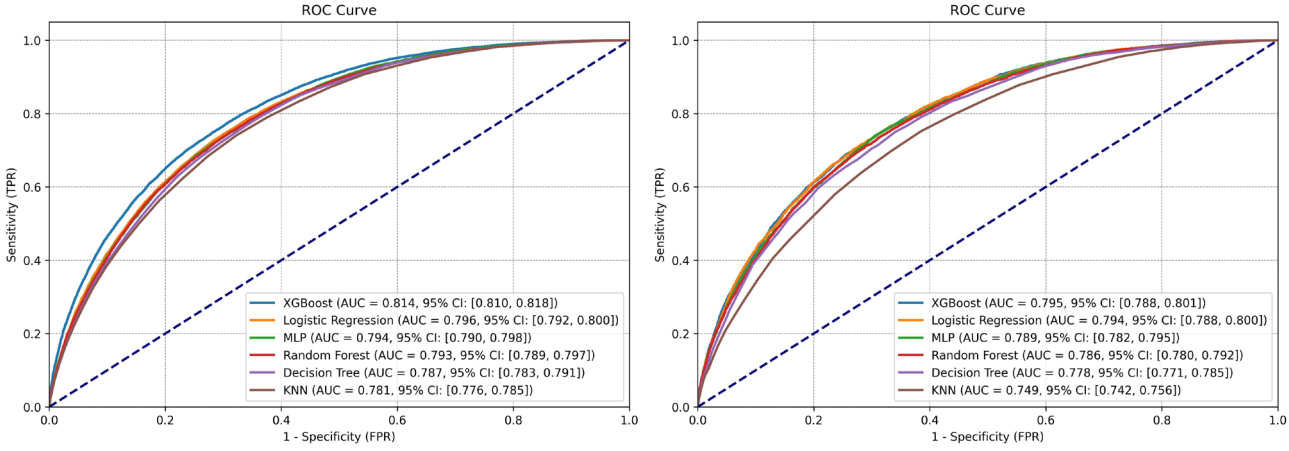


Figure 1. *ROC curves of the machine learning models. Left: Training set; Right: Test set. AUC values of the machine learning models presented with 95% CI. ROC: Receiver Operating Characteristics, AUC: Area Under Curve, KNN: K-Nearest Neighbors, MLP: Multi-Layer Perceptron, XGBoost: eXtreme Gradient Boosting*

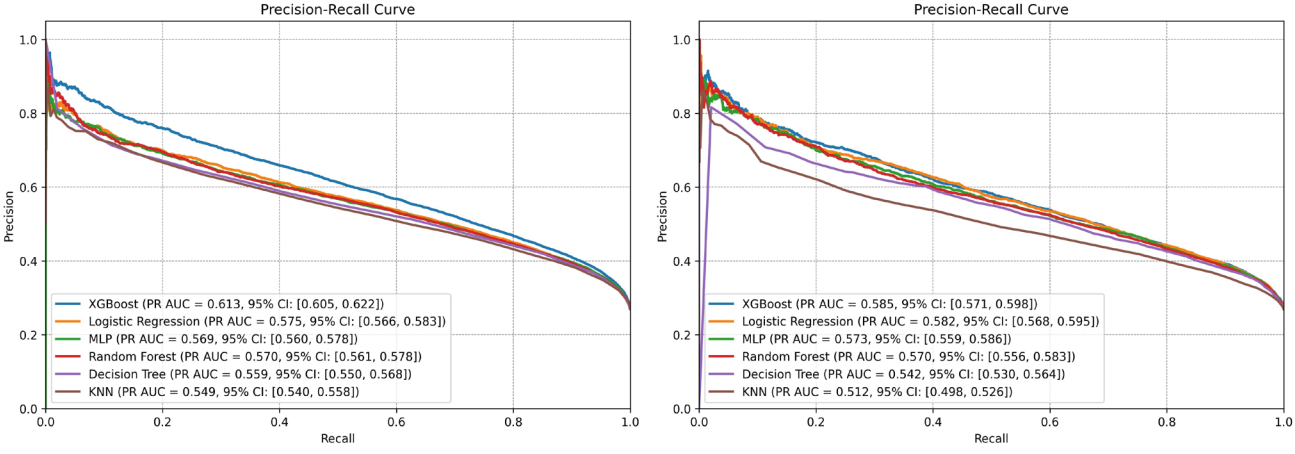


Figure 2. *PR curves of the machine learning models. Left: Training set; Right: Test set. PR AUC values of the machine learning models presented with 95% CI. PR AUC: Precision-Recall Area Under Curve, KNN: K-Nearest Neighbors, MLP: Multi-Layer Perceptron, XGBoost: eXtreme Gradient Boosting*

Table II. *The performances of the machine learning models Figure 2*

	Training set (n= 54406)								**Test set (n=23318)**							
	AUC	PR AUC	MCC	Kappa	Accuracy	Precision	Recall	F1-Score	AUC	PR AUC	MCC	Kappa	Accuracy	Precision	Recall	F1-Score
XGBoost	0.814 (0.810 – 0.818)	0.613 (0.605 – 0.622)	0.418 (0.412 – 0.431)	0.392 (0.380 – 0.415)	0.715 (0.703 – 0.739)	0.482 (0.468 – 0.511)	0.775 (0.723 – 0.800)	0.594 (0.588 – 0.602)	0.795 (0.788 – 0.801)	0.585 (0.571 – 0.598)	0.388 (0.379 – 0.409)	0.363 (0.346 – 0.397)	0.701 (0.682 – 0.734)	0.466 (0.448 – 0.507)	0.752 (0.685 – 0.788)	0.575 (0.567 – 0.587)
Logistic Regression	0.796 (0.792 – 0.800)	0.575 (0.566 – 0.583)	0.399 (0.390 – 0.408)	0.378 (0.357 – 0.389)	0.712 (0.689 – 0.722)	0.478 (0.454 – 0.490)	0.743 (0.725 – 0.794)	0.582 (0.575 – 0.588)	0.794 (0.788 – 0.800)	0.582 (0.568 – 0.595)	0.392 (0.379 – 0.407)	0.373 (0.350 – 0.393)	0.713 (0.686 – 0.729)	0.478 (0.450 – 0.499)	0.727 (0.697 – 0.790)	0.577 (0.568 – 0.587)
MLP	0.794 (0.790 – 0.798)	0.569 (0.560 – 0.578)	0.393 (0.384 – 0.402)	0.371 (0.352 – 0.386)	0.709 (0.686 – 0.723)	0.474 (0.452 – 0.491)	0.740 (0.712 – 0.788)	0.578 (0.571 – 0.584)	0.789 (0.782 – 0.795)	0.573 (0.559 – 0.586)	0.390 (0.378 – 0.402)	0.367 (0.353 – 0.380)	0.706 (0.692 – 0.713)	0.471 (0.455 – 0.481)	0.742 (0.730 – 0.771)	0.576 (0.567 – 0.585)
Random Forest	0.793 (0.789 – 0.797)	0.570 (0.561 – 0.578)	0.393 (0.384 – 0.401)	0.369 (0.352 – 0.379)	0.705 (0.687 – 0.716)	0.470 (0.452 – 0.483)	0.750 (0.728 – 0.787)	0.578 (0.572 – 0.584)	0.786 (0.780 – 0.792)	0.570 (0.556 – 0.583)	0.379 (0.368 – 0.394)	0.356 (0.337 – 0.378)	0.699 (0.677 – 0.721)	0.463 (0.441 – 0.488)	0.737 (0.693 – 0.787)	0.569 (0.561 – 0.579)
Decision Tree	0.787 (0.783 – 0.791)	0.559 (0.550 – 0.568)	0.381 (0.374 – 0.390)	0.352 (0.339 – 0.369)	0.690 (0.677 – 0.709)	0.455 (0.440 – 0.475)	0.766 (0.727 – 0.795)	0.571 (0.565 – 0.577)	0.778 (0.771 – 0.785)	0.542 (0.530 – 0.564)	0.365 (0.353 – 0.377)	0.338 (0.320 – 0.352)	0.684 (0.662 – 0.701)	0.448 (0.430 – 0.465)	0.750 (0.713 – 0.795)	0.561 (0.552 – 0.570)
KNN	0.781 (0.776 – 0.785)	0.549 (0.540 – 0.558)	0.374 (0.366 – 0.381)	0.350 (0.334 – 0.357)	0.694 (0.671 – 0.698)	0.458 (0.439 – 0.465)	0.741 (0.734 – 0.788)	0.566 (0.560 – 0.572)	0.749 (0.742 – 0.756)	0.512 (0.498 – 0.526)	0.326 (0.314 – 0.338)	0.293 (0.283 – 0.316)	0.652 (0.646 – 0.680)	0.419 (0.410 – 0.444)	0.752 (0.693 – 0.763)	0.538 (0.528 – 0.546)

AUC: Area Under Curve, KNN: K-Nearest Neighbours, MCC: Matthews correlation coefficient, MLP: Multi-Layer Perceptron, PR AUC: Precision-Recall Area Under Curve, XGBoost: eXtreme Gradient Boosting

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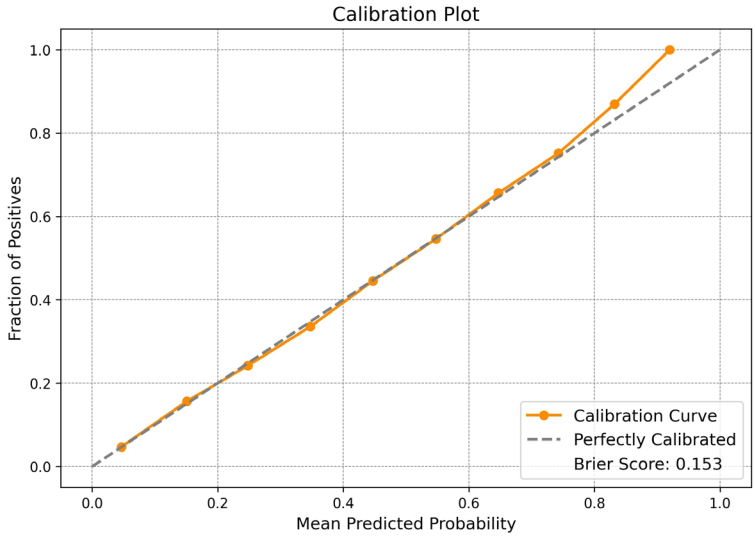


Figure 3. *Calibration plot of the XGBoost model*

Model Interpretation

SHAP analysis results of the XGBoost model are presented in Figure 4. According to the SHAP analysis, the presence of hypertension has the highest contribution to the prediction of IHD in patients with diabetes mellitus.

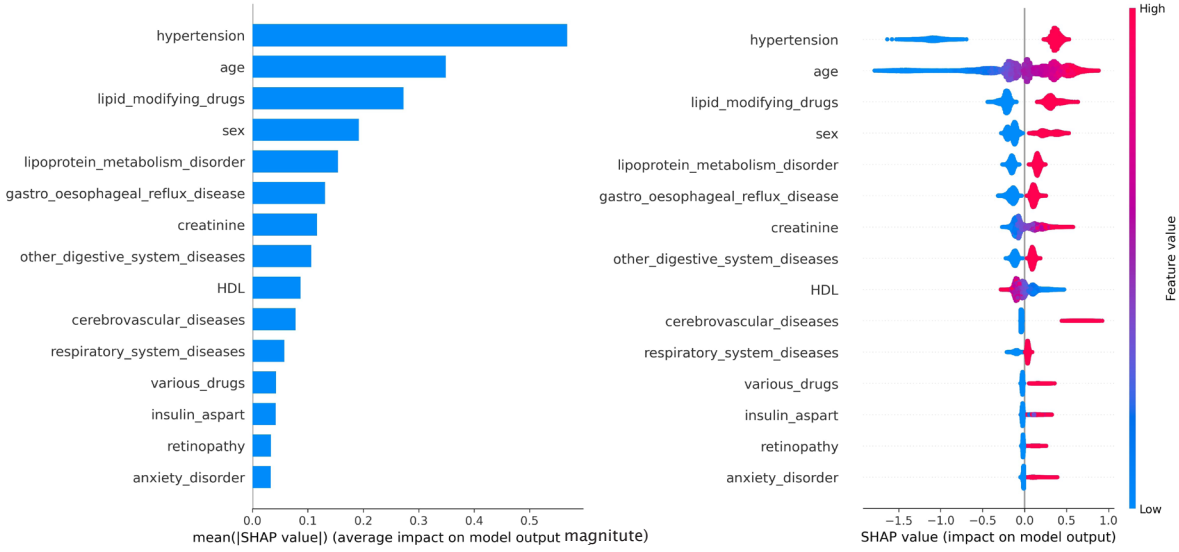


Figure 4. *SHAP analysis of the XGBoost model. Left: SHAP bar plot; Right: SHAP summary dot plot, HDL: High-density lipoprotein SHAP: SHapley Additive exPlanations*

4. DISCUSSION

According to the study results, XGBoost had superior performance with an AUC of 0.814 (95% CI: 0.810 – 0.818) on the training set and 0.795 (95% CI: 0.788 – 0.801) on the test set. The calibration plot for the XGBoost model showed a close alignment with the 45-degree line of perfect prediction and it achieved 0.153 Brier score. Additionally, XGBoost achieved a recall of 0.752 (95% CI: 0.685 – 0.788) and a precision of 0.466 (95% CI: 0.448 – 0.507) on the test set. The relatively high recall indicates that the model is effective in identifying patients with IHD and correctly classifying approximately 75% of true positive cases. However, the relatively low precision indicates a considerable false positive rate, which may lead to

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unnecessary diagnostic procedures. These findings suggest that while XGBoost is promising for detecting IHD in patients with diabetes mellitus, further optimization may be needed to improve precision and reduce false positives.

Relevant literature on the prediction of cardiovascular events in diabetic patients has reported AUC values ranging from 0.62 to 0.83 [13-17]. Among these studies, random forest was reported as the best-performing model in three studies [14-16]. While this finding highlights the effectiveness of random forest in predicting cardiovascular events in diabetic patients, neural network approaches have also demonstrated strong predictive performance in medicine for various tasks [32]. However, in our study, XGBoost outperformed random forest and MLP, indicating that model performance may vary depending on the dataset and study setting. Additionally, among the relevant studies, only one study conducted an external validation [16]. Most of the studies evaluated performance using internal test sets, which may limit the generalizability of prediction models across diverse populations.

In addition to machine learning models, several traditional risk scores have been developed to predict cardiovascular events. While some of these scores were developed for the general population, others were specifically developed for diabetic patients. The Framingham Risk Score, DECODE Risk Score, Prospective Cardiovascular Münster (PROCAM) Score, Systematic Coronary Risk Evaluation (SCORE), and Myocardial Infarction Population Registry of Girona (REGICOR) were developed for the general population [33]. In contrast, the United Kingdom Prospective Diabetes Study (UKPDS) Risk Engine, the Swedish National Diabetes Register (NDR) Score, and the ADVANCE Risk Model were specifically developed for diabetic patients [33]. According to a recent systematic review and meta-analysis, machine learning outperformed conventional risk scores in predicting cardiovascular disease [34]. The pooled AUC for conventional risk scores was reported as 0.765 (95% CI: 0.734 – 0.796) [34]. In comparison, our XGBoost model achieved a higher AUC of 0.814 (95% CI: 0.810 – 0.818) on the training set and 0.795 (95% CI: 0.788 – 0.801) on the test set. Notably, our results were obtained in a specific population with diabetic patients. Therefore, the model performance may have been affected by being developed and evaluated within the more homogeneous and clinically relevant subgroup.

To understand the structure of the prediction model and analyze the contribution of the features to the predictions, we interpreted the XGBoost model using SHAP analysis. Among 15 key variables that were found to be the important predictors of IHD in diabetic patients, the presence of hypertension at the first line of the list is expectable. Hypertension is one of the main risk factors for IHD, particularly in patients with diabetes mellitus [35-37]. Older age and male sex were also significant predictors of IHD [38, 39]. Furthermore, low high-density lipoprotein (HDL) levels were related to an increased risk of IHD, consistent with the literature that identifies low HDL as a significant risk factor for both IHD and cerebrovascular diseases, especially in older patients with diabetes mellitus [40]. On the other hand, lipid modifying drugs are widely used to prevent cardiovascular diseases and may reflect an underlying risk profile for IHD [41]. Lipoprotein metabolism disorders were also associated with increased IHD risk [42]. Retinopathy, digestive system diseases, anxiety, respiratory system diseases, and cerebrovascular diseases may not be direct causes of IHD. However, their presence may indicate the overall burden of comorbidities and vascular dysfunction, both of which contribute to increased cardiovascular disease [43, 44]. Moreover, various drugs and insulin aspart were significant predictors of IHD in diabetic patients. The presence of various drugs or insulin therapy may reflect the management of diabetes mellitus or additional comorbidities, which may increase the risk of cardiovascular disease [43, 45-47]. Increased creatinine, a sign of deteriorated renal function, was another significant predictor of IHD. This suggests that reduced renal function is associated with higher IHD risk [48]. Finally, gastroesophageal reflux disease was one of the significant predictors of IHD. Gastroesophageal reflux disease has been reported as a risk factor for cardiovascular disease, which might be due to shared risk factors such as body mass index, HDL cholesterol, triglycerides, smoking, type 2 diabetes, and insomnia [49].

The main limitation of our study is the lack of external validation. Although our prediction models demonstrated promising performance on the internal test set, they were not evaluated using an external dataset. Therefore, the generalizability of our prediction models to the different populations remains uncertain. The same limitation was observed in most of the related studies. However, our use of population-level data may provide better generalizability compared to models developed from single institution or hospital-level data. Future studies should be conducted in diverse populations to develop more robust and generalizable models. Additionally, the patients with IHD in our dataset have already been diagnosed. Our model may not perform well in identifying patients with early-stage IHD.

Conclusion

In conclusion, the study results demonstrate the potential of machine learning for predicting IHD in patients with diabetes mellitus. The findings of the study suggest that machine learning models can support the identification of IHD in a high-risk population. Furthermore, the integration of machine learning models into hospital information systems could enable real-time decision support for clinicians. However, limitations of current models should be addressed, especially external validation across diverse populations to ensure the generalizability of the machine learning models.

Compliance with Ethical Standards

Ethical approval: The ethical approval for this study was obtained from Akdeniz University, School of Medicine, Clinical Scientific Research Ethics Committee (date: 31.10.2024, approval number: TBAEK-698). The informed consent was not required for this study since the study used a publicly available dataset that was anonymized and complied with ethical and legal standards.

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Author contributions: NI, SO and KHG: Conceptualization, NI: Formal analysis, NI, SO and KHG: Investigation, NI and KHG: Methodology, NI: Software, NI: Visualization, NI: Writing – original draft, KHG: Writing – review and editing. All authors have approved the final version of the manuscript.

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Supplementary Document

1. Input variables

Demographics: Sex, Age

Laboratory tests: HbA1c, HDL, Creatinine

Comorbidities: Infectious diseases (A00-B99), Malignant neoplasms (C00-C97), Obesity (E66), Thyroid diseases (E00-E07), In situ neoplasms, benign neoplasms, neoplasms of uncertain or unknown behavior (D00-D48), Anemia (D50-D64), Vitamin deficiencies (E50-E56), Disorders of lipoprotein metabolism and other lipidemias (E78), Other Endocrine disorders (E00-E90, excluding E00-E07, E10-E14, E50-E56, E66 and E78), Depression (F32, F33, F92), Anxiety disorder (F41), Other mental disorders (F00-F99, excluding F31, F32, F33, F41, and F92), Other neuropathies (G56-G63, excluding G63.2), Diabetic Polyneuropathy (G63.2), Other nervous system disorders (G00-G99, excluding G56-G63), Cataract (H25 and H26), Retinopathies (H30-H36), Disorders of refraction and accommodation (H52), Impacted cerumen (H61.2), Tinnitus (H93.1), Other eye diseases (H00-H59, excluding H25, H26, H30-H36, H52), Otitis Externa (H60), Other diseases of ear and mastoid process (H60-H95, excluding H60, H61.2, H93.1), Hypertension (I10), Cerebrovascular diseases (I60-I69), Diseases of the respiratory system (J00-J99), Diseases of oral cavity, salivary glands and jaws (K00-K14), Gastro-oesophageal reflux disease (K21), Functional dyspepsia (K30), Other diseases of the digestive system (K00-K93, excluding K00-K14, K21, K30), Diseases of the skin and subcutaneous tissue (L00-L99), Diseases of the musculoskeletal system and connective tissue (M00-M99), Renal failure (N17-N19), Other diseases of the genitourinary system (N20-N99)

Drugs: Some alimentary tract preparations (A01, A07, A09) (digestive_drugs), Vitamins, supplements, tonics, anabolic agents, appetite etimulants (A11-A16) (other_digestive), Lipid modifying agents (C10), Dermatologicals (D), Genitourinary system (G01, G02, G04), Sex hormones (G03), Systemic endocrine preparations (H1-H3), Systemic antiinfectives (J01-J05), Vaccines (J07), Muskuloskeletal system (M), Antiepileptics (N03), Antipsychotics (N05A), Anxiolytics (N05B), Other nervous system drugs (N07), Antiparasitic products, insecticides and repellents (P), Respiratory system (R), Sensory organs (S), Various (V), Acarbose (per 1 gr/year), Dapagliflozin (per 1 gr/year), Exenatide (per 1 gr/year), Gliclazide (per 1 gr/year), Glimepiride (per 1 gr/year), Glipizide (per 1 gr/year), Insulin aspart (per 1000U/year), Insulin detemir (per 1000U/year), Insulin glargine (per 1000U/year), Insulin glulisine (per 1000U/year), Insulin lispro (per 1000U/year), Insulin lente (per 1000U/year), Insulin regular (per 1000U/year), Linagliptin (per 1 gr/year), Metmorfin (per 1 kg/year), Nateglinide (per 1 gr/year), Pioglitazone (per 1 gr/year), Repaglinide (per 1 gr/year), Saxagliptin (per 1 gr/year), Sitagliptin (per 1 gr/year), Vildagliptin (per 1 gr/year)

2. The descriptive statistics of the dataset

	Overall (n=77724)	Ischemic heart diseases		P value
		Present (n=20932)	Absent (n=56792)	
Sex				
Female	51735 (66.6)	12204 (58.3)	39531 (69.6)	<0.001[a]
Male	25989 (33.4)	8728 (41.7)	17261 (30.4)	
Infectious diseases (A00-B99)				
Present	25609 (32.9)	7636 (36.5)	17973 (31.6)	<0.001[a]
Absent	52115 (67.1)	13296 (63.5)	38819 (68.4)	
Malignant neoplasms (C00-C97)				
Present	3286 (4.2)	1034 (4.9)	2252 (4.0)	<0.001[a]
Absent	74438 (95.8)	19898 (95.1)	54540 (96.0)	
Obesity (E66)				
Present	3471 (4.5)	737 (3.5)	2734 (4.8)	<0.001[a]
Absent	74253 (95.5)	20195 (96.5)	54058 (95.2)	
Thyroid diseases (E00-E07)				
Present	20271 (26.1)	5403 (25.8)	14868 (26.2)	0.300[a]
Absent	57453 (73.9)	15529 (74.2)	41924 (73.8)	
In situ neoplasms, benign neoplasms, neoplasms of uncertain or unknown behavior (D00-D48)				
Present	3673 (4.7)	1071 (5.1)	2602 (4.6)	0.002[a]
Absent	74051 (95.3)	19861 (94.9)	54190 (95.4)	
Anemia (D50-D64)				

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Present	28303 (36.4)	8656 (41.4)	19647 (34.6)	<0.001[a]
Absent	49421 (63.6)	12276 (58.6)	37145 (65.4)	
Vitamin deficiencies (E50-E56)				
Present	28045 (36.1)	8148 (38.9)	19897 (35.0)	<0.001[a]
Absent	49679 (63.9)	12784 (61.1)	36895 (65.0)	
Disorders of lipoprotein metabolism and other lipidemias (E78)				
Present	42508 (54.7)	15271 (73.0)	27237 (48.0)	<0.001[a]
Absent	35216 (45.3)	5661 (27.0)	29555 (52.0)	
Other Endocrine disorders (E00-E90, excluding E00-E07, E10-E14, E50-E56, E66 and E78)				
Present	20325 (26.2)	5875 (28.1)	14450 (25.4)	<0.001[a]
Absent	57399 (73.8)	15057 (71.9)	42342 (74.6)	
Depression (F32, F33, F92)				
Present	16399 (21.1)	5499 (26.3)	10900 (19.2)	<0.001[a]
Absent	61325 (78.9)	15433 (73.7)	45892 (80.8)	
Anxiety disorder (F41)				
Present	13256 (17.1)	4474 (21.4)	8782 (15.5)	<0.001[a]
Absent	64468 (82.9)	16458 (78.6)	48010 (84.5)	
Other mental disorders (F00-F99, excluding F31, F32, F33, F41, and F92)				
Present	4653 (6.0)	1611 (7.7)	3042 (5.4)	<0.001[a]
Absent	73071 (94.0)	19321 (92.3)	53750 (94.6)	
Other neuropathies (G56-G63, excluding G63.2)				
Present	11716 (15.1)	3872 (18.5)	7844 (13.8)	<0.001[a]
Absent	66008 (84.9)	17060 (81.5)	48948 (86.2)	
Diabetic Polyneuropathy (G63.2)				
Present	13475 (17.3)	4593 (21.9)	8882 (15.6)	<0.001[a]
Absent	64249 (82.7)	16339 (78.1)	47910 (84.4)	
Other nervous system disorders (G00-G99, excluding G56-G63)				
Present	14944 (19.2)	5316 (25.4)	9628 (17.0)	<0.001[a]
Absent	62780 (80.8)	15616 (74.6)	47164 (83.0)	
Cataract (H25 and H26)				
Present	4409 (5.7)	1756 (8.4)	2653 (4.7)	<0.001[a]
Absent	73315 (94.3)	19176 (91.6)	54139 (95.3)	
Retinopathies (H30-H36)				
Present	10872 (14.0)	4101 (19.6)	6771 (11.9)	<0.001[a]
Absent	66852 (86.0)	16831 (80.4)	50021 (88.1)	
Disorders of refraction and accommodation (H52)				
Present	22325 (28.7)	6496 (31)	15829 (27.9)	<0.001[a]
Absent	55399 (71.3)	14436 (69)	40963 (72.1)	
Impacted cerumen (H61.2)				
Present	4448 (5.7)	1502 (7.2)	2946 (5.2)	<0.001[a]
Absent	73276 (94.3)	19430 (92.8)	53846 (94.8)	
Tinnitus (H93.1)				
Present	2486 (3.2)	862 (4.1)	1624 (2.9)	<0.001[a]
Absent	75238 (96.8)	20070 (95.9)	55168 (97.1)	
Other eye diseases (H00-H59, excluding H25, H26, H30-H36, H52)				
Present	27965 (36.0)	8775 (41.9)	19190 (33.8)	<0.001[a]
Absent	49759 (64.0)	12157 (58.1)	37602 (66.2)	
Otitis Externa (H60)				

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Present	3788 (4.9)	1102 (5.3)	2686 (4.7)	0.002[a]
Absent	73936 (95.1)	19830 (94.7)	54106 (95.3)	
Other diseases of ear and mastoid process (H60-H95, excluding H60, H61.2, H93.1)				
Present	9253 (11.9)	3145 (15.0)	6108 (10.8)	<0.001[a]
Absent	68471 (88.1)	17787 (85.0)	50684 (89.2)	
Hypertension (I10)				
Present	56932 (73.2)	19890 (95.0)	37042 (65.2)	<0.001[a]
Absent	20792 (26.8)	1042 (5.0)	19750 (34.8)	
Cerebrovascular diseases (I60-I69)				
Present	4967 (6.4)	2830 (13.5)	2137 (3.8)	<0.001[a]
Absent	72757 (93.6)	18102 (86.5)	54655 (96.2)	
Diseases of the respiratory system (J00-J99)				
Present	54583 (70.2)	15778 (75.4)	38805 (68.3)	<0.001[a]
Absent	23141 (29.8)	5154 (24.6)	17987 (31.7)	
Diseases of oral cavity, salivary glands and jaws (K00-K14)				
Present	21690 (27.9)	5943 (28.4)	15747 (27.7)	0.067[a]
Absent	56034 (72.1)	14989 (71.6)	41045 (72.3)	
Gastro-oesophageal reflux disease (K21)				
Present	37813 (48.7)	12978 (62.0)	24835 (43.7)	<0.001[a]
Absent	39911 (51.3)	7954 (38.0)	31957 (56.3)	
Functional dyspepsia (K30)				
Present	14440 (18.6)	4690 (22.4)	9750 (17.2)	<0.001[a]
Absent	63284 (81.4)	16242 (77.6)	47042 (82.8)	
Other diseases of the digestive system (K00-K93, excluding K00-K14, K21, K30)				
Present	40954 (52.7)	13181 (63.0)	27773 (48.9)	<0.001[a]
Absent	36770 (47.3)	7751 (37.0)	29019 (51.1)	
Diseases of the skin and subcutaneous tissue (L00-L99)				
Present	32968 (42.4)	10036 (47.9)	22932 (40.4)	<0.001[a]
Absent	44756 (57.6)	10896 (52.1)	33860 (59.6)	
Diseases of the musculoskeletal system and connective tissue (M00-M99)				
Present	60529 (77.9)	17362 (82.9)	43167 (76.0)	<0.001[a]
Absent	17195 (22.1)	3570 (17.1)	13625 (24.0)	
Renal failure (N17-N19)				
Present	6296 (8.1)	3077 (14.7)	3219 (5.7)	<0.001[a]
Absent	71428 (91.9)	17855 (85.3)	53573 (94.3)	
Other diseases of the genitourinary system (N20-N99)				
Present	36959 (47.6)	10629 (50.8)	26330 (46.4)	<0.001[a]
Absent	40765 (52.4)	10303 (49.2)	30462 (53.6)	
Some alimentary tract preparations (A01, A07, A09) (digestive_drugs)				
Present	26476 (34.1)	7543 (36.0)	18933 (33.3)	<0.001[a]
Absent	51248 (65.9)	13389 (64.0)	37859 (66.7)	
Vitamins, supplements, tonics, anabolic agents, appetite etimulants (A11-A16) (other_digestive)				
Present	48210 (62.0)	13909 (66.4)	34301 (60.4)	<0.001[a]
Absent	29514 (38.0)	7023 (33.6)	22491 (39.6)	
Lipid modifying agents (C10)				
Present	36654 (47.2)	14027 (67.0)	22627 (39.8)	<0.001[a]
Absent	41070 (52.8)	6905 (33.0)	34165 (60.2)	
Dermatologicals (D)				

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Present	39764 (51.2)	11713 (56.0)	28051 (49.4)	<0.001[a]
Absent	37960 (48.8)	9219 (44.0)	28741 (50.6)	
Genitourinary system (G01, G02, G04)				
Present	13540 (17.4)	4388 (21.0)	9152 (16.1)	<0.001[a]
Absent	64184 (82.6)	16544 (79.0)	47640 (83.9)	
Sex hormones (G03)				
Present	3001 (3.9)	516 (2.5)	2485 (4.4)	<0.001[a]
Absent	74723 (96.1)	20416 (97.5)	54307 (95.6)	
Systemic endocrine preparations (H1-H3)				
Present	20492 (26.4)	5657 (27.0)	14835 (26.1)	0.011[a]
Absent	57232 (73.6)	15275 (73.0)	41957 (73.9)	
Systemic antiinfectives (J01-J05)				
Present	51723 (66.5)	14640 (69.9)	37083 (65.3)	<0.001[a]
Absent	26001 (33.5)	6292 (30.1)	19709 (34.7)	
Vaccines (J07)				
Present	6530 (8.4)	2842 (13.6)	3688 (6.5)	<0.001[a]
Absent	71194 (91.6)	18090 (86.4)	53104 (93.5)	
Muskuloskeletal system (M)				
Present	59600 (76.7)	16714 (79.8)	42886 (75.5)	<0.001[a]
Absent	18124 (23.3)	4218 (20.2)	13906 (24.5)	
Antiepileptics (N03)				
Present	13947 (17.9)	4857 (23.2)	9090 (16.0)	<0.001[a]
Absent	63777 (82.1)	16075 (76.8)	47702 (84.0)	
Antipsychotics (N05A)				
Present	4184 (5.4)	1267 (6.1)	2917 (5.1)	<0.001[a]
Absent	73540 (94.6)	19665 (93.9)	53875 (94.9)	
Anxiolytics (N05B)				
Present	2918 (3.8)	1026 (4.9)	1892 (3.3)	<0.001[a]
Absent	74806 (96.2)	19906 (95.1)	54900 (96.7)	
Other nervous system drugs (N07)				
Present	6514 (8.4)	2364 (11.3)	4150 (7.3)	<0.001[a]
Absent	71210 (91.6)	18568 (88.7)	52642 (92.7)	
Antiparasitic products, insecticides and repellents (P)				
Present	7708 (9.9)	2000 (9.6)	5708 (10.1)	0.040[a]
Absent	70016 (90.1)	18932 (90.4)	51084 (89.9)	
Respiratory system (R)				
Present	52109 (67.0)	15146 (72.4)	36963 (65.1)	<0.001[a]
Absent	25615 (33.0)	5786 (27.6)	19829 (34.9)	
Sensory organs (S)				
Present	27206 (35.0)	8615 (41.2)	18591 (32.7)	<0.001[a]
Absent	50518 (65.0)	12317 (58.8)	38201 (67.3)	
Various (V)				
Present	8308 (10.7)	3188 (15.2)	5120 (9.0)	<0.001[a]
Absent	69416 (89.3)	17744 (84.8)	51672 (91.0)	
Age	57 (49-65)	63 (56-69)	55 (47-63)	<0.001[b]
HbA1c	7.2 (6.3-8.8)	7.3 (6.4-8.71)	7.2 (6.2-8.8)	<0.001[b]
HDL	46 (39-54)	44 (37-52)	46.26 (39-55)	<0.001[b]
Creatinine	0.76 (0.65-0.91)	0.84 (0.70-1.04)	0.74 (0.63-0.87)	<0.001[b]
Acarbose (per 1 gr/year)*	0.003±0.015	0.004±0.017	0.003±0.014	<0.001[b]

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Dapagliflozin (per 1 gr/year)*	0.112±0.493	0.109±0.489	0.113±0.494	0.194[b]
Exenatide (per 1 gr/year)*	0.039±0.413	0.037±0.399	0.040±0.418	0.170[b]
Gliclazide (per 1 gr/year)*	4.133±9.948	4.512±10.583	3.993±9.700	0.002[b]
Glimepiride (per 1 gr/year)*	0.018±0.145	0.025±0.170	0.016±0.134	<0.001[b]
Glipizide (per 1 gr/year)*	0.004±0.128	0.005±0.154	0.003±0.117	0.047[b]
Insulin aspart (per 1000U/year)*	1.468±3.935	1.980±4.558	1.280±3.661	<0.001[b]
Insulin detemir (per 1000U/year)*	1.002±3.877	1.245±4.431	0.912±3.649	<0.001[b]
Insulin glargine (per 1000U/year)*	2.518±5.817	3.149±6.461	2.285±5.543	<0.001[b]
Insulin glulisine (per 1000U/year)*	0.212±1.224	0.269±1.405	0.191±1.150	<0.001[b]
Insulin lispro (per 1000U/year)*	0.368±1.944	0.459±2.179	0.334±1.849	<0.001[b]
Insulin lente (per 1000U/year)*	0.064±1.102	0.088±1.376	0.055±0.982	0.212[b]
Insulin regular (per 1000U/year)*	0.134±1.477	0.114±1.360	0.141±1.518	0.035[b]
Linagliptin (per 1 gr/year)*	0.069±0.273	0.080±0.293	0.065±0.266	<0.001[b]
Metmorfin (per 1 kg/year)*	0.390±0.323	0.386±0.333	0.391±0.320	<0.001[b]
Nateglinide (per 1 gr/year)*	0.003±0.018	0.003±0.018	0.003±0.017	0.255[b]
Pioglitazone (per 1 gr/year)*	0.942±2.910	0.780±2.664	1.002±2.994	<0.001[b]
Repaglinide (per 1 gr/year)*	0.023±0.189	0.028±0.205	0.021±0.182	<0.001[b]
Saxagliptin (per 1 gr/year)*	0.036±0.208	0.036±0.210	0.036±0.207	0.324[b]
Sitagliptin (per 1 gr/year)*	1.767±6.392	1.843±6.567	1.738±6.325	0.165[b]
Vildagliptin (per 1 gr/year)*	1.455±5.959	1.465±5.991	1.451±5.948	0.926[b]
[a]: *Chi Square Test*				
[b]: *Mann Whitney U Test*				
*: *Represented as mean±sd due to 0 percentile values.*				

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