Cardiovascular Diabetology

RESEARCH

Open Access

Predicting major adverse cardiac events in diabetes and chronic kidney disease: a machine learning study from the Silesia Diabetes-Heart Project

Hanna Kwiendacz[1†], Bi Huang[2,3†], Yang Chen[2†], Oliwia Janota[1,4], Krzysztof Irlik[1,2], Yang Liu[2,5], Marta Mantovani[2,6], Yalin Zheng[2,7], Mirela Hendel[8], Julia Piaśnik[8], Wiktoria Wójcik[8], Uazman Alam[2,9], Janusz Gumprecht[1], Gregory Y. H. Lip[2,10†] and Katarzyna Nabrdalik[1,2*†]

Abstract

Background People living with diabetes mellitus (DM) and chronic kidney disease (CKD) are at significantly high risk of cardiovascular events (CVEs), however the predictive performance of traditional risk prediction methods are limited.

Methods We utilised machine learning (ML) model to predict CVEs in persons with DM and CKD from the Silesia Diabetes-Heart Project, a routine standard of care dataset. CVEs were defined as composite of nonfatal myocardial infarction, new onset heart failure, nonfatal stroke, incident atrial fibrillation, undergoing percutaneous coronary intervention or coronary artery bypass grafting, hospitalisation or death due to cardiovascular disease. Five ML models (Logistic regression [LR], Random forest [RF], Support vector classification [SVC], Light gradient boosting machine [LGBM], and eXtreme gradient boosting machine [XGBM]) were constructed. The predictive performance of the five ML models was compared and the model interpretability were evaluated by Shapley Additive exPlanations (SHAP).

Results A total of 1,116 people with DM and CKD out of 3,056 with DM were included (median age 67 [IQR 57–76] years; 57% men). The incidence of CVEs was 14.1% (157/1,116) during a median of 3.1 years follow-up period. Ten important features were identified through univariate Logistic regression, Boruta, and Least Absolute Shrinkage and Selection Operator [LASSO] regression. Among the five ML models based on these features, LGBM had the highest area under curve [AUC] (AUC = 0.740, 95% Confidence Interval [CI] 0.738–0.743), followed by LR (AUC = 0.621, 95% CI 0.618–0.623), RF (AUC = 0.707, 95% CI 0.704–0.709), SVC (AUC = 0.707, 95% CI 0.704–0.710), and XGBM (AUC = 0.710, 95% CI 0.707–0.713). Meanwhile, LGBM had relatively higher Recall (0.739), F1-score (0.820), and G-mean (0.826). The SHAP plot of LGBM revealed that estimated glomerular filtration rate (eGFR), age, and triglyceride glucose index were the three most important features for predicting CVEs.

[†]Joint first authors: Hanna Kwiendacz, Bi Huang and Yang Chen

[†]Joint senior authors: Gregory Y. H. Lip and Katarzyna Nabrdalik

*Correspondence:
Katarzyna Nabrdalik
knabrdalik@sum.edu.pl

Full list of author information is available at the end of the article

Conclusion Ten features-based ML models, especially the LGBM model, had acceptable performance in predicting CVEs in persons with DM and CKD. A decrease in eGFR, aging, and elevated inflammatory markers significantly enhanced the predictive capability of the model. Future external validation of our model is required prior to implementation in a clinical environment.

Keywords Diabetes mellitus, Chronic kidney disease, Cardiovascular events, Machine learning

Introduction

Chronic kidney disease (CKD) is a common complication in people living with diabetes mellitus (DM), affecting approximately 40% of them [1]. More importantly, their co-existence is associated with multiplicative adverse effects on cardiovascular (CV) outcomes, including premature death [2]. Due to the high number of persons with DM and CKD who are at risk of CV disease (CVD) and CV events (CVEs), early and improved strategies to ascertain and mitigate risk are required.

However, the phenotypes of persons with DM and CKD are highly heterogeneous, making traditional prediction methods limited in their effectiveness [3, 4], such that there are significant challenges in identifying people for optimization of treatment. Although previous studies have established some models using traditional statistical methods, their predictive power was modest [5–7]. Therefore, it is important to explore new methods to predict outcomes in people with DM and CKD.

In recent years, artificial intelligence has been widely used not only in the diagnosis and treatment of CVD but also in predicting clinical outcomes [8]. Machine learning (ML) is a branch of artificial intelligence that provides machines the ability to automatically learn from data to identify patterns and make predictions [9]. Compared with traditional prediction methods, ML has the capability to analyse complex, nonlinear relationships among a wide range of clinical, demographic, and laboratory variables, potentially enabling more precise risk stratification; additionally, ML algorithms can dynamically learn from new data, enabling real-time updates to predictions [10]. Previous studies have used ML to predict CVEs in persons with DM or CKD alone [11–14], but studies focusing on the prediction of CVEs in people with DM and concomitant CKD are limited. Personalised medicine could improve management of persons with DM and CKD but to do so, an accurate and interpretable predictive model is needed.

Considering these needs, the aim of present study was to explore the development and interpretability ML model to predict the CVEs in patients with DM and CKD coming from the Silesia Diabetes Heart Project.

Methods

Study design

The design of the Silesia Diabetes-Heart Project (ClinicalTrials.gov, NCT05626413) has been previously reported [12]. Briefly, this is a single-center, observational, prospective cohort study which enrolled persons with DM hospitalised in the Department of Internal Medicine and Diabetology in Zabrze, Poland between January 2015 and March 2023. The study protocol was approved by the Medical University of Silesia Ethics Committee (PCN/0022/KB/126/20) and was conducted in accordance with the Declaration of Helsinki.

The eligibility criterion was the presense of DM irrespective of the etiology. The main exclusion criteria were end-stage cancer or death during hospitalisation. Baseline characteristics including demographic data, medical histories, vital signs on admission, laboratory test results, and medication used during hospitalisation were recorded. The definitions of each comorbidity and the protocols of the laboratory test were as reported previously [12].

Follow-up and endpoints

Patients' follow-up was conducted between March 2021 and November 2023 via phone contact with the patient or patient's relatives to determine whether any new CVEs event occurred after patient's discharge. The detailed date of each event was gathered. The endpoint of the present study was the composite of CVEs defined as composite of nonfatal myocardial infarction, new onset heart failure, nonfatal stroke, incident atrial fibrillation, undergoing percutaneous coronary intervention or coronary artery bypass grafting, hospitalisation or death due to CVD.

Participants in ML analysis

The participants in the present study were persons with DM and concomitant CKD. The diagnosis of CKD was defined as persistently decreased estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2, or persistently elevated urine albumin excretion (UAE) ≥ 30 mg/g, or both, for more than 3 months. Our ML analysis aimed to establish a predictive model based on clinical variables to stratify persons at high risk of CVEs through: (1) constructing ML models to separate two classifications of persons: those who underwent CVEs and those who were free of CVEs during follow-up period; (2) evaluating the predictive performance of the ML models; (3) visualizing the results of ML to make them interpretable.

Feature selection for ML analysis

In the predesigned case report form, a total of 81 variables were included. For ML analysis, variables with missing values exceeding 20% of the total number were excluded and the remaining missing values were dealt with multiple imputations. Then collinearity analysis was used to evaluate the correlations among the variables. If two variables had significant collinearity with Spearman correlation > 0.6, one of which was not further taken into the feature selection in order to avoid collinearity, and the principle of variable selection was based on the clinical importance of the variables.

The whole group of persons with DM and CKD was randomly split into a training and validation cohort with a ratio of 7:3. Then univariate Logistic analysis, Boruta, and Least absolute shrinkage and selection operator (LASSO) regression were used to screen the features for ML analysis. A univariate Logistic analysis is a classic variable selection method based on P values and variables with P value < 0.05 were regarded as statistically significant. The Boruta algorithm is a feature ranking and selection algorithm based on random forests algorithm [15] and LASSO regression is a type of regularization method that penalizes with L1-norm [16]. The final features used for ML analysis were based on the three screening methods, and meanwhile taking the clinical importance into consideration.

Construction of ML models and performance evaluation

In the present study, based on model diversity and representation, performance across different data type, robustness and handling of overfitting, and practical applicability, we constructed five ML models including Logistic regression (LR), Randomforest (RF), Support vector classification (SVC), Light gradient boosting machine (LGBM), and eXtreme gradient boosting machine (XGBM). For each model, hyperparameters were optimised and early stopping was employed during training where possible, using 5-fold cross-validation on training data. Due to the imbalance between number of events and non-events, sample weight was used when constructing these models.

The main predictive performance of ML models was evaluated by receiver operating characteristic curve (ROC) with the mean area under curve (AUC) and 95% confidence interval (CI) of each classifier using 1,000 bootstrapping iterations in the validation cohort. Besides, the accuracy, specificity, sensitivity, precision, recall, F1-score, and G mean for each classifier were calculated.

Model interpretability

The model interpretability was performed by Shapley Additive exPlanations (SHAP) [17], a method used to explain the output of ML models with SHAP value, which was used for measuring global and local feature importance, dependence, and interaction among different variables as well as visualizing the features for given observations.

Statistical analysis

In the original dataset, variables with more than 20% missing values were discarded; for other variables with missing values, multiple imputation with 'mice' package (version 3.16.0) in R. Continuous variables were expressed with median and interquartile range (IQR) and were compared with Mann-Whitney U tests due to the non-normal distribution characteristics. Categorical variables were expressed with counts and percentages, and were compared with Fisher's exact test or Chi-square test.

The split of the whole dataset into *training and testing cohorts* and the feature selection with univariate Logistic analysis, Boruta, and LASSO regression were conducted by R (version 4.3.3, Austria). The ML algorithms, evaluation of predictive performance, and visualization of the LGBM model with SHAP were implemented via Python (version 3.11.5). A two-tailed P value < 0.05 was considered statistically significant.

Results

Characteristics of the studied cohort

Among the 3,056 people with DM, 719 had no outcome data and 27 had missing UAE value. Among the remaining 2,310 individuals, 1,194 had eGFR > 60 ml/min and UAE < 30 mg/g, and finally 1,116 people with CKD and DM were included in the present study (Fig. 1).

During a median of 3.1 (IQR 2.1–4.1) years follow-up period, the incidence of CVEs was 14.1% (157/1,116) (Supplement Table 1). Baseline characteristics are shown in Table 1. The median age of patients in this cohort was 67 (IQR 57–76) years and 57% were men. Compared with people without CVEs, those with CVEs were older, more likely to be female, and had higher prevalence of comorbidities including hypertension, coronary artery disease (CAD), prior stroke, generalised atherosclerosis, heart failure, and hyperuricemia (all $P < 0.05$). Compared with participants without CVEs, people with CVEs tended to be type 2 DM (94% vs. 86%, $P = 0.009$), with a higher incidence of diabetic retinopathy (41% vs. 33%, $P = 0.043$), and lower eGFR (median 55 vs. 58 ml/min/1.73 m^2, $P = 0.008$). The fasting blood glucose was comparable between the two groups, but persons without CVEs had a higher haemoglobin A1c (HbA1c) (median 8.8% vs. 8.4%, $P = 0.027$). The use of glucose lowering drugs including insulin and oral drugs were similar in the two groups. Beta blockers, aspirin, clopidogrel, and loop diuretics were used more often in persons with CVEs (all $P < 0.05$).

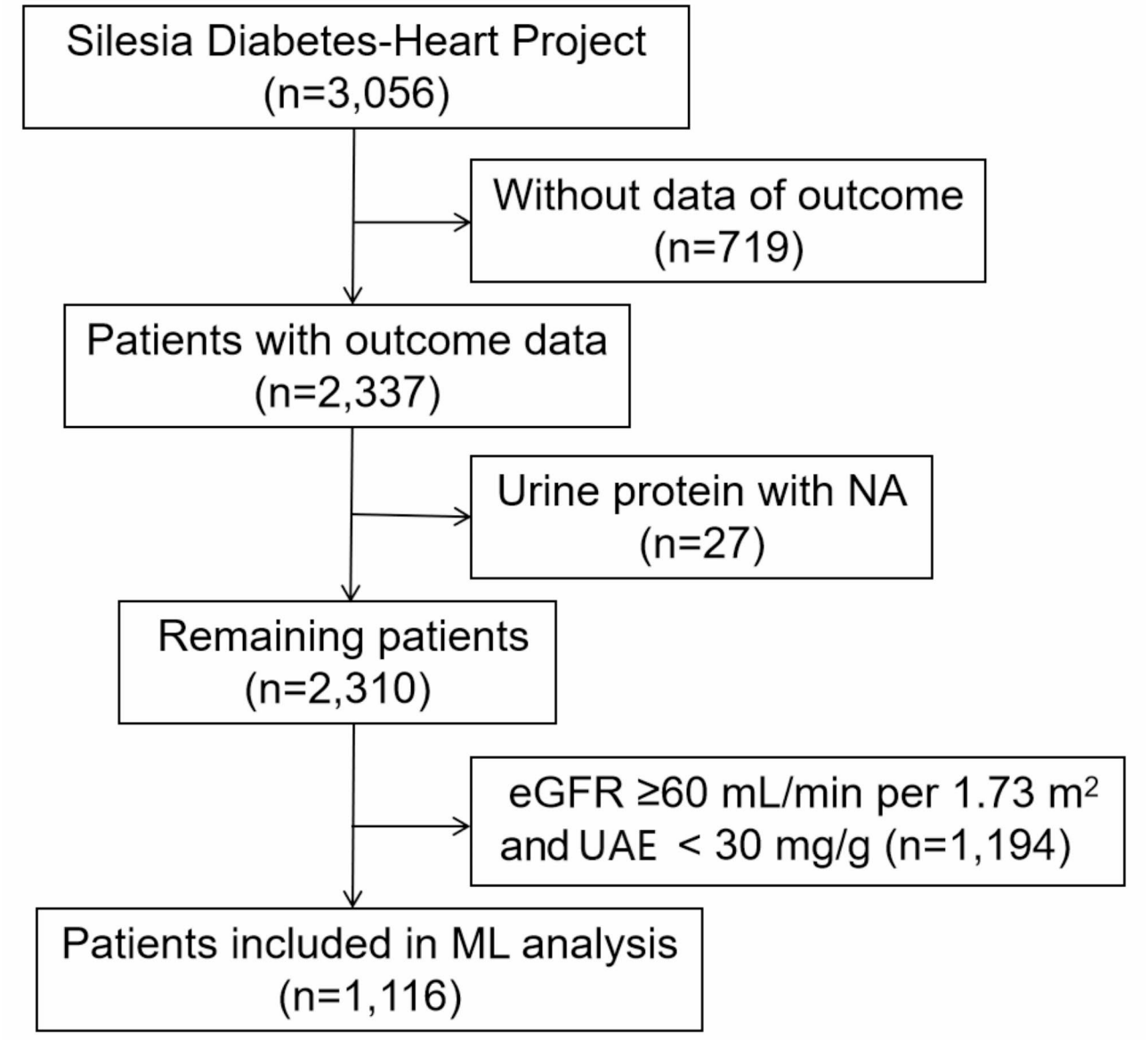

Fig. 1 Study flowchart. eGFR, estimated glomerular filtration rate; NA, not available; UAE, urine albumin excretion

Feature selection for ML

Among the 81 variables in the initial dataset, seven variables (low density lipoprotein, high density lipoprotein, non-high density lipoprotein, triglyceride to high density lipoprotein ratio, metabolic score for insulin resistance (METS) of the first day, and METS of the last day, and atherogenic index) were discarded due to relatively high missing values. Then collinearity was tested among the remaining variables and a Spearman correlation > 0.6 between two variables was considered as significant collinearity. After excluding 43 variables with significant collinearity, 31 variables were finally taken into the process of feature selection (Supplement Fig. 1).

The dataset was randomly split into a training and testing cohort with a ratio of 7:3. All the compared parameters were comparable between training and testing cohort (all $P > 0.05$). Baseline characteristics of training and testing group are presented in Supplement Table 2.

Three methods were used to screen the features. Univariate Logistic analysis identified 13 variables (Supplement Table 3). The results of Boruta and LASSO regression analysis were shown in Fig. 2. Eight variables (age, eGFR, CAD, heart failure, triglyceride glucose [TyG] index, and hypertension) were confirmed and six variables (history of stroke, haemoglobin A1c [HbA1c], gender, CRP [C-reactive protein], fibrosis 4 score, and uric acid) were tentative (Fig. 2A). In the LASSO regression, 12 variables were selected as potential predictors (age, gender, eGFR, CAD, heart failure, HbA1c, CRP,

Table 1 Baseline characteristics of the study group

Characteristics	All patients ($n=1,116$)	Without CVEs ($n=959$)	With CVEs ($n=157$)	*P* value*
Age (years)	67 (57, 76)	67 (56, 76)	70 (62, 78)	0.003
Male (n, %)	639 (57%)	562 (59%)	77 (49%)	0.025
BMI (kg/m^2)	31 (26, 35)	31 (26, 35)	32 (27, 37)	0.055
Hypertension (n, %)	908 (81%)	767 (80%)	141 (90%)	0.003
CAD (n, %)	462 (41%)	376 (39%)	86 (55%)	< 0.001
History of stroke (n, %)	120 (11%)	95 (9.9%)	25 (16%)	0.024
Generalized atherosclerosis (n, %)	606 (54%)	502 (52%)	104 (66%)	0.001
Atrial fibrillation (n, %)	145 (13%)	121 (13%)	24 (15%)	0.4
Heart failure (n, %)	292 (26%)	236 (25%)	56 (36%)	0.003
PAD (n, %)	60 (5.4%)	48 (5.0%)	12 (7.6%)	0.2
Hyperlipidaemia (n, %)	733 (66%)	629 (66%)	104 (66%)	0.9
Hyperuricemia (n, %)	508 (46%)	425 (44%)	83 (53%)	0.046
Current smoker (n, %)	211 (19%)	180 (19%)	31 (20%)	0.8
Type 2 DM (n, %)	973 (87%)	826 (86%)	147 (94%)	0.009
Duration of DM (years)	22 (17, 29)	22 (16, 29)	22 (20, 29)	0.054
Diabetic retinopathy (n, %)	376 (34%)	312 (33%)	64 (41%)	0.043
Diabetic foot (n, %)	46 (4.1%)	37 (3.9%)	9 (5.7%)	0.3
Diabetic peripheral neuropathy (n, %)	94 (8.4%)	77 (8.0%)	17 (11%)	0.2
SBP (mmHg)	130 (120, 140)	130 (120, 139)	130 (122, 140)	0.2
DBP (mmHg)	76 (70, 80)	76 (70, 80)	77 (70, 80)	0.6
HR (bpm)	80 (75, 90)	80 (75, 90)	80 (75, 90)	0.9
WBC (x10^9/L)	8.6 (6.9, 10.9)	8.7 (6.9, 10.9)	8.5 (6.8, 10.9)	0.5
Haemoglobin (g/dL)	13.30 (11.90, 14.70)	13.40 (12.00, 14.80)	12.80 (11.40, 14.00)	0.001
eGFR (ml/min)	57 (41, 82)	58 (41, 84)	55 (40, 70)	0.008
TC (mmol/L)	4.25 (3.42, 5.21)	4.26 (3.48, 5.27)	4.00 (3.26, 5.06)	0.084
LDL (mmol/L)	2.12 (1.50, 2.88)	2.13 (1.50, 2.88)	2.07 (1.49, 2.75)	0.8
TyG index	9.41 (8.94, 9.96)	9.43 (8.95, 9.96)	9.31 (8.89, 9.96)	0.7
CRP (mg/L)	5 (2, 17)	5 (2, 17)	6 (2, 22)	0.12
HbA1c (%)	8.66 (7.10, 10.40)	8.78 (7.11, 10.50)	8.40 (6.81, 9.91)	0.027
Fasting blood glucose (mg/dL)	173 (135, 230)	176 (135, 230)	164 (134, 230)	0.9
Uric acid (mg/dL)	350 (272, 432)	345 (270, 429)	373 (286, 448)	0.024
Serum sodium (mmol/L)	139.0 (136.0, 141.0)	139.0 (136.0, 141.0)	139.0 (136.0, 141.0)	0.5
Serum potassium (mmol/L)	4.59 (4.26, 4.98)	4.58 (4.25, 4.98)	4.61 (4.29, 5.08)	0.4
Urine albumin excretion > 30 mg/g	825 (74%)	718 (75%)	107 (68%)	0.076
FIB-4	1.17 (0.73, 1.74)	1.16 (0.70, 1.72)	1.35 (0.86, 1.93)	0.021
Insulin	831 (74%)	712 (74%)	119 (76%)	0.7
Metformin	490 (44%)	420 (44%)	70 (45%)	0.9
Sulfonylureas	290 (26%)	249 (26%)	41 (26%)	> 0.9
SGLT2 inhibitors	137 (12%)	121 (13%)	16 (10%)	0.4
GLP1R agonists	37 (3.3%)	31 (3.2%)	6 (3.8%)	0.7
DPP4 inhibitors	173 (16%)	152 (16%)	21 (13%)	0.4
RAAS inhibitors	575 (52%)	494 (52%)	81 (52%)	> 0.9
CCB	423 (38%)	364 (38%)	59 (38%)	> 0.9
Beta blocker	713 (64%)	591 (62%)	122 (78%)	< 0.001
Alpha blocker	166 (15%)	139 (14%)	27 (17%)	0.4
Aspirin	606 (54%)	505 (53%)	101 (64%)	0.006
Clopidogrel	67 (6.0%)	52 (5.4%)	15 (9.6%)	0.043
VKA	41 (3.7%)	35 (3.6%)	6 (3.8%)	> 0.9
NOACs	107 (9.6%)	92 (9.6%)	15 (9.6%)	> 0.9
Statin	646 (58%)	547 (57%)	99 (63%)	0.2
Fibrate	26 (2.3%)	20 (2.1%)	6 (3.8%)	0.2
Amiodarone	11 (1.0%)	11 (1.1%)	0 (0%)	0.4

Table 1 (continued)

Characteristics	All patients (*n* = 1,116)	Without CVEs (*n* = 959)	With CVEs (*n* = 157)	*P* value*
Digoxin	26 (2.3%)	22 (2.3%)	4 (2.5%)	0.8
Loop diuretics	482 (43%)	395 (41%)	87 (55%)	< 0.001

*Compared between group with CVEs and group without CVEs

CAD, coronary artery disease; CCB, calcium channel blockers; CRP, C-reactive protein; DBP, diastolic blood pressure; DM, diabetes mellitus; DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis 4 score; GLP1R, glucagon-like peptide-1 receptor; HbA1c, haemoglobin A1c; HR, heart rate; LDL, low-density lipoprotein; NOACs, non-vitamin K oral anticoagulants; PAD, peripheral artery disease; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; SGLT2, sodium-glucose cotransporters 2; TC, total cholesterol; TyG, triglyceride glucose; VKA, vitamin K antagonist; WBC, white blood cell

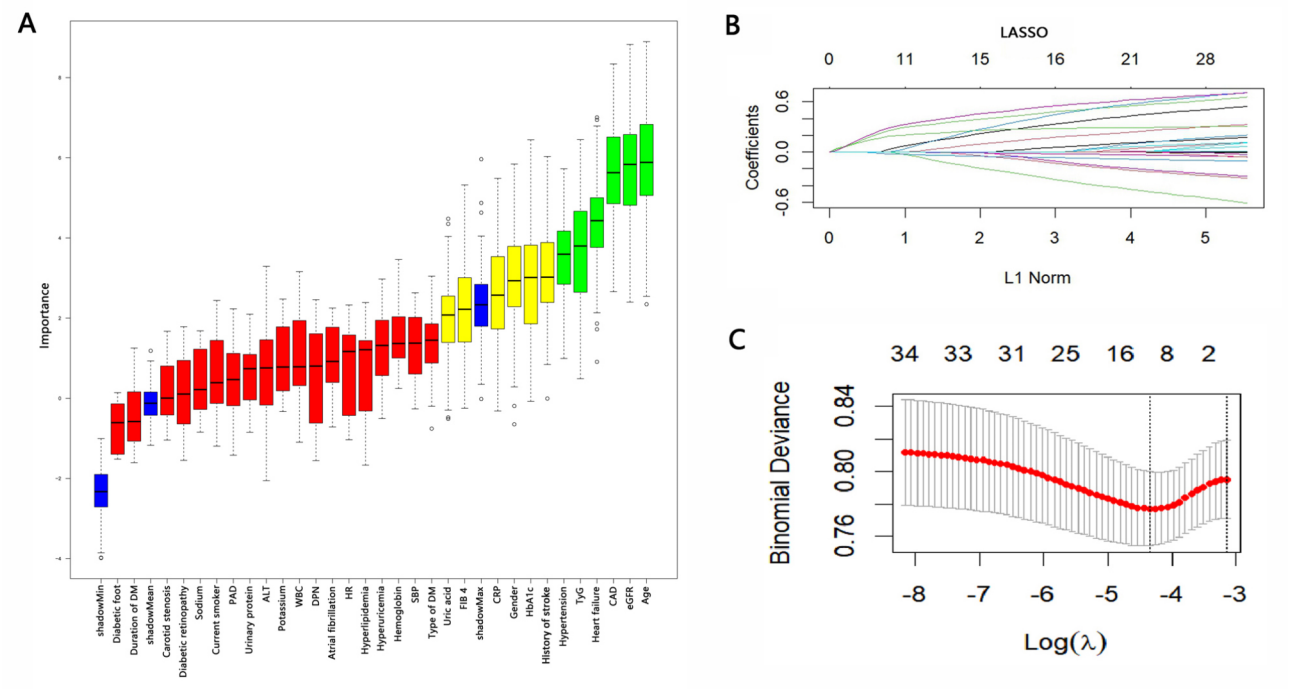

Fig. 2 Feature selection with Boruta and LASSO regression. **A** The blue plot shows minimum, average, and max shadow score. Variables having box plot in green are important, in yellow as tentative, and in red as rejected; **B** The correlation between L1 norm and different coefficients in LASSO regression. L1 norm is the regularisation term for LASSO; **C** The correlation between lamda with binomial deviance. There are two dashed lines in the graph. The left dashed line indicates the minimum mean squared error while the right one indicates one standard error away from the minimum mean squared error. ALT, alanine aminotransferase; CAD, coronary artery disease; CRP, C-reactive protein; DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis 4 score; HbA1c, haemoglobin A1c; HR, heart rate; PAD, peripheral artery disease; SBP, systolic blood pressure; TyG, triglyceride glucose; WBC, white blood cell

TyG index, hypertension, haemoglobin, history of stroke, and heart rate) and the optimal number of variables was 10 (Fig. 2B and C). Based on the features selected from the three methods and considering clinical importance, we ultimately selected 10 features (age, gender, eGFR, HbA1c, CAD, TyG index, heart failure, CRP, hypertension, history of stroke) for ML analysis.

Evaluation of ML models

The ROCs of the five ML models are shown in Fig. 3. Among the five ML models, LGBM model had the highest AUC (0.740, 95% CI 0.738–0.743), while RF, SVC, and XGBM models had similar AUCs (RF, 0.707, 95% CI 0.704–0.709; SVC, 0.707, 95% CI 0.704–0.710; XGBM, 0.710, 95% CI 0.707–0.713). LR had the lowest AUC (0.621, 95% CI 0.618–0.623). Other metrics of the five ML models are shown in Table 2, among which LGBM model had relatively higher accuracy (0.723), specificity (0.739), precision (0.923), and F1 score (0.820).

Model interpretability

Due to the fact that LGBM model had the best prediction performance among the five ML models, it was chosen to interpret the model's output. The feature importance based on LGBM model is shown in Supplement Fig. 2. The most important five features were age, followed by eGFR, then CRP, TyG index, and HbA1c.

The SHAP values provided more insights into how LGBM mode predicted the outcome. Feature importance summarised by the SHAP summary plot are displayed in Fig. 4. The three most important feature are eGFR, followed by age and TyG index where lower eGFR, higher

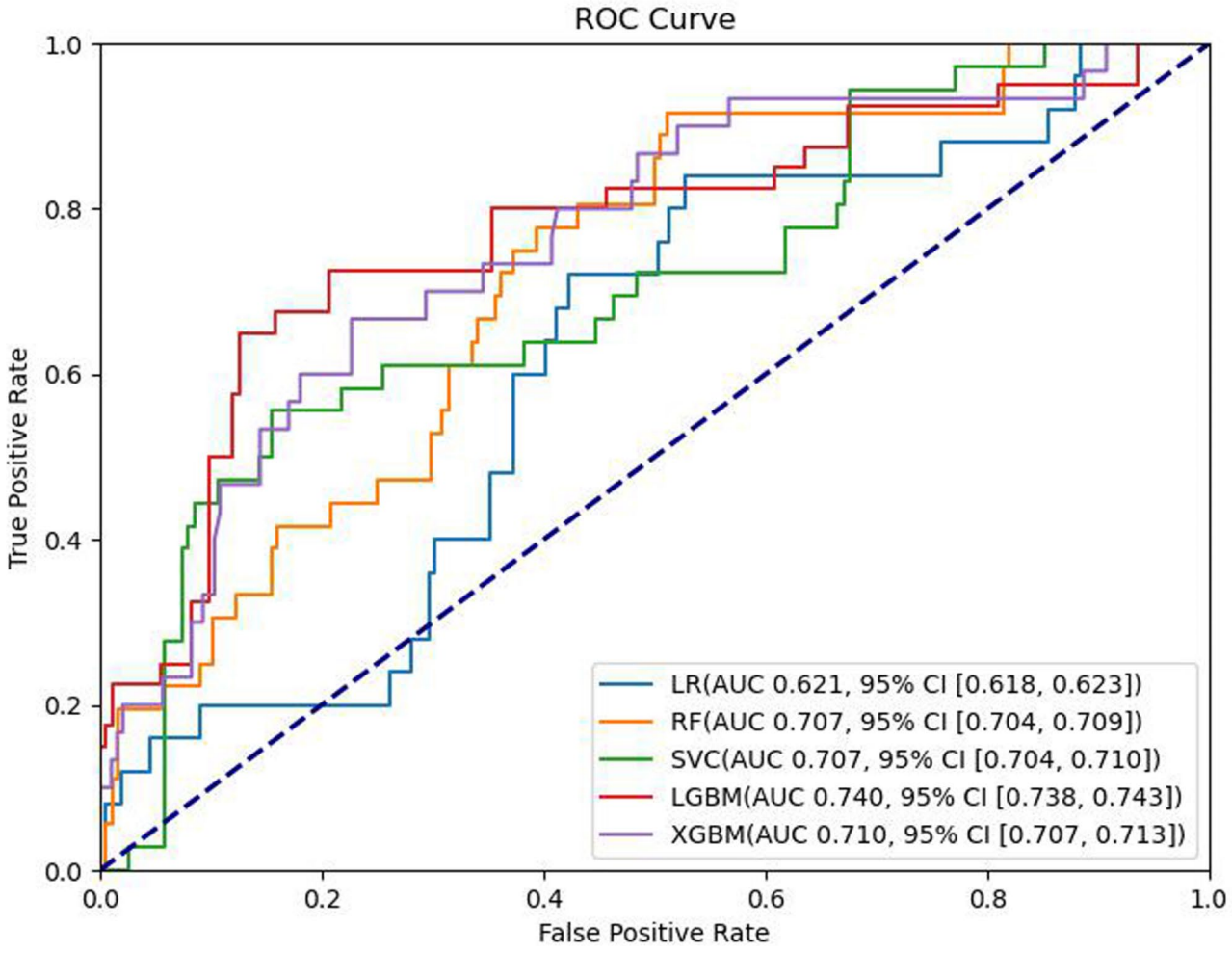

Fig. 3 The ROCs for predicting CVEs of different ML models. AUC, area under curve; LGBM, Light gradient boosting machine; LR, Logistic regression; RF, Random forest; SVC, Support vector classification; XGBM, eXtreme gradient boosting machine

Table 2 Comparison of the performance of the ML models

ML models	AUC (95% CI)	Accuracy	Specificity	Sensitivity	Precision	Recall	F1-score	G-mean
LR	0.621 (0.618–0.623)	0.590	0.589	0.596	0.899	0.589	0.711	0.727
RF	0.707 (0.704–0.709)	0.714	0.540	0.540	0.909	0.742	0.816	0.821
SVC	0.707 (0.704–0.710)	0.686	0.614	0.698	0.918	0.698	0.792	0.800
LGBM	0.740 (0.738–0.743)	0.723	0.739	0.624	0.923	0.739	0.820	0.826
XGBM	0.710 (0.707–0.713)	0.695	0.572	0.631	0.860	0.673	0.755	0.601

LGBM, Light gradient boosting machine; LR, Logistic regression; ML, machine learning; RF, Random forest; SVC, Support vector classification; XGBM, eXtreme gradient boosting machine

age and higher TyG index are associated with increased model's interpretability.

The interaction and dependence of three most important feature (eGFR, age, and TyG index) and the top seven features are shown in Supplement Fig. 3. A representative sample was chosen to depict the output with force plots, which illustrated how the SHAP values explained individual model features (Supplement Fig. 4). Each feature had different impact on the predicted probability of the outcome, which together determined the final contribution of these features (Supplement Fig. 4A). A decision plot of 20 representative observations visualised how each feature in each sample contributed to the overall prediction (Supplement Fig. 4B).

Discussion

The outcomes of this large prospective cohort of persons with DM demonstrate the following: (i); five ML models, especially the LGBM, based on ten patients' related features had acceptable performance in predicting CVEs in

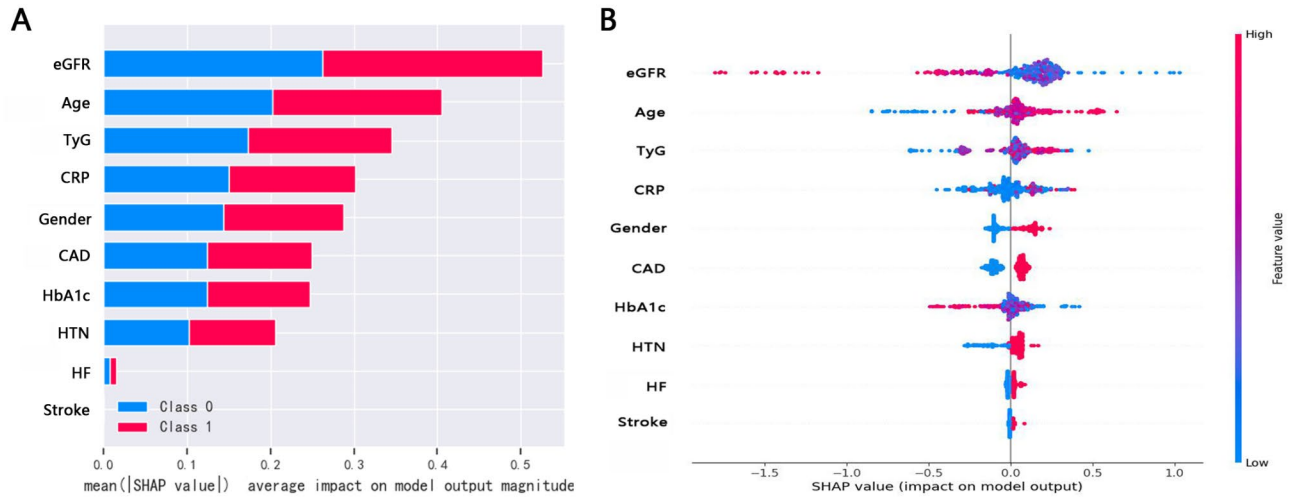

Fig. 4 The importance of features and their contribution to the output with SHAP value evaluation. **A** The importance of the ten features was shown in descending order and in two matrixes, Class 0 and Class 1, representing negative and positive classification, respectively; **B** SHAP beeswarm plot to interpret the contribution of each feature with red color increasing the interpretability while blue color decreasing the interpretability. CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HF, heart failure; HTN, hypertension; TyG, triglyceride glucose index. Stroke means history of stroke

people with DM and CKD; (ii) the key factors in interpretation of CVEs model prediction were eGFR, age, and TyG index; (iii) lower eGFR, higher age and TyG index increased the interpretation of the model.

In the previous analysis related to The Silesia Diabetes-Heart Project [12], RUSBoost algorithm with multiple Logistic regression was utilised to predict the CVEs in persons with DM and found that using 12 selected features could correctly identify 74% high-risk persons and 62.4% low-risk ones with an AUC of 0.72. Meanwhile, unsupervised hierarchical clustering used in this study revealed distinct characteristics between high and low risk persons, indicating ML had the potential in risk stratification for persons with DM.

For persons with CKD, studies also demonstrated that ML had good predictive performance for predicting CVEs [11]. However, these studies focused either only on DM or CKD alone, and seldom studies were specifically designed to evaluate the role of ML in predicting CVEs in persons with DM and concomitant CKD. For example, Ren et al. [18] recently conducted a retrospective study to assess the risk of CVEs with a deep learning-based survival model (DeepSurv) in diabetic kidney disease and found DeepSurv model had a relatively high predictive performance with AUC of 0.780, but the duration of this study was relatively short with a median follow-up of 10.4 months. In contrast, the median follow-up period in our present study was greater than five years. Given that both DM and CKD are chronic conditions and their interaction worsens the outcome, a longer follow-up period helps to better assess the factors related to prognosis.

The performance of ML algorithms is based largely on the quality and quantity of available data. In this study, we first performed feature selection using three commonly used and classic methods to select feature variables for ML and the selected variables from the three methods were similar. This suggests that although the principles of the three feature selection methods differ, the results are robust. The common features from these methods include most of these parameters (namely, age, CAD, CRP, eGFR, gender, HbA1c, hypertension, heart failure, history of stroke and TyG index).

There are several ML models and algorithms, each has its own advantages [19]. For example, the LR model is easy to implement, performs well on low-dimensional data, and is very efficient for linear data. However, it does not achieve good accuracy when variables have complex relationships [20]. The RF model scales well with large datasets, achieves high accuracy with several decision trees, and is robust to noise, but it can suffer from overfitting if the model captures noise in the training data. Thus, leading to poor generalization on new data and a lack of interpretability; in contrast, the Support Vector Machine (SVM) model is more robust compared to the LR model, performs well in classifying semi-structured or unstructured data, and has less risk of overfitting, but it is not suitable for large datasets with many features or datasets with missing values [20]. Since each model is based on a different algorithm, their performance varies across different datasets. The best approach is to use cross-validation to determine which model performs best on the test data. In our study we constructed five ML models and evaluated their predictive performance. Among these, LGBM model had the best performance. LGBM is a gradient boosting framework based on decision tree algorithm with faster training speed, higher efficiency,

and better accuracy than any other boosting algorithm, such as XGBM [21]. However, the performance of different ML models varies significantly, and the optimal ML model should be based on the quality and quantity of the study's data as well as the optimised algorithms with optimal hyperparameters.

ML algorithms operate as 'black boxes', as such it may be unclear how they produce a certain decision output [22]. In recent years, the explainable ML model was proposed to make the black-box model to be of greater accuracy and high interpretable with different methods, among which SHAP is a commonly used tool [23]. SHAP is a game theoretic approach based upon Shapley values, which quantifies the contribution of each feature to the outcome of the ML model and explains how each feature contributes to the predicted probability and displays the final prediction based on the sum of the average prediction and all the SHAP values; therefore, SHAP is helpful not only to the local interpretation of the model, but also for global interpretation, thus making the model more explainable [24–26]. It's worth noting that the feature importances obtained from LGBM and SHAP demonstrated some differences. For instance, the most important feature in the former is age, while in the latter, the most important feature is eGFR. This discrepancy might be related to the different algorithms used by the two methods: LGBM model uses the Gain or Split algorithm [27], whereas SHAP value is based on tree-based models [28]. However, overall, the feature importances calculated by the two methods are similar, indicating that these features contribute consistently across different algorithms. Additionally, whilst using SHAP to interpret the machine learning model, we discovered some unexpected findings. For example, elevated HbA1c levels are typically associated with poor glycemic control and an increased risk of CVEs [29]. However, our study found that lower SHAP values of HbA1c enhanced the model's interpretability. A possible interpretation is that lower HbA1c levels indicate stricter glycemic control, which to some extent increases the risk of hypoglycemia and may also correspondingly elevate the risk of CVEs [30]. Therefore, when developing ML models in the future, incorporating hypoglycemic events and their severity may be a key feature in CVE prediction.

Most of prior ML studies of DM and CKD only provide features selection [18, 31–33], but seldom delve into the decision-making processes with an explainable method. Our present study displays the underlying process of prediction; how variables contribute to the decision as well as the relationships of interdependence and interaction between variables, making the ML model justifiable and transparent. Based on the SHAP value, the top three features in the present study were eGFR, age, and TyG and there was a dependent relationship among the three variables. Lower eGFR and higher age increased the interpretation of the model while higher eGFR and younger age decreased the interpretation, which are consistent with the conclusion from traditional prediction algorithm [34, 35].

In recent years, TyG index, a composite indicator composed of fasting triglyceride and fasting glucose, has been shown to be an alternative proxy of insulin resistance [36]. TyG index has also been demonstrated to be a reliable predictor of CVEs in both general population and people with DM [37, 38]. Besides, the predictive value of TyG index has been confirmed in people with CKD [39]. Our present study extends previous findings, indicating that TyG index was also an important marker of predicting CVEs in concomitant DM and CKD.

We constructed five ML models, but the predictive ability of the optimal model (LGBM) was only moderate with AUC 0.740. DM and CKD involve complex pathophysiological process and clinical characteristics are significantly heterogeneous among individuals while collecting all features is challenging; therefore, the features used for ML model may not be generalised to all individuals. Importantly, the predictive performance of our ML is multifactorial dependent. Besides clinical features, the algorithm differences among different ML models, model complexity, and hyperparameters used in the model altogether determine the final performance.

In this 'real world' clinical study we used non-traditional method, ML model to predict CVEs in persons with DM and CKD. This novel approach identified several features for predicting CVEs, some of which have been widely validated, while some new features and their clinical value warrants further investigation. For persons with DM and CKD, whether treatment strategies could be optimised based on the risk stratification with ML model and whether their prognosis could be improved deserve further study.

Limitations

Some limitations in the present study need to be addressed. First, the sample size of persons with CKD in this large cohort of persons with DM is relatively modest and the incidence of events is relatively low. These unbalanced data are challenging for ML. Although weights were introduced for correction in the ML parameter design, the characteristics of the cohort may limit the predictive performance. Second, the study granular lacks features related to cardiac structure and function, such as B-type natriuretic peptide, troponin, and left ventricular ejection fraction, which could add important variables for CVEs. However, the addition of these variables in routine clinical practice would be challenging, given the variability to which they are undertaken. Third, the significant heterogeneity in clinical characteristics among persons

with DM and CKD reduces the predictive performance of ML. Fourth, we only constructed five commonly used ML models, and it is unclear whether other models may have better predictive performance. In addition, SHAP, as a method for interpreting the results of ML models, has its limitations. SHAP method itself does not assume feature independence, some approximation methods used to calculate SHAP values do rely on this assumption [40]; in most real-world applications, this assumption is unlikely to hold, and as such, SHAP-based explanations should be interpreted with caution. Additionally, interpreting SHAP values can be particularly challenging in high-dimensional datasets. Moreover, a significant limitation of SHAP analysis is that it does not quantify the importance of predictors in the context of real-world problems but rather their relevance to the model's predictions [40]. SHAP values illustrate how features influence the model's predictions for specific observations, rather than how those features contribute to the actual outcomes. Finally, this study lacks external validation, so it needs to be further confirmed whether the model can be generalised to new cohorts and therefore, results of the present study should be interpreted with caution as a proof-of-concept. Future research should be directed at incorporating or refining the current methodology and parameters of importance with routinely collected retinal fundus imaging data to ascertain whether such a model is superior to the currently described ML-based models. Indeed, our team has recently demonstrated the ability of a novel AI-based algorithm to detect cardiovascular autonomic neuropathy in DM utilising retinal fundus images [41]. The importance being that cardiovascular autonomic neuropathy is highly predictive of CVEs in DM [42].

Conclusion

We demonstrate an interpretable CVEs risk prediction ML model for people with DM and CKD. Ten features-based ML models had acceptable performance in predicting CVEs in persons with DM and CKD, with the best performing being the LGBM model. Among the features, a decrease in eGFR, aging, and elevated inflammatory markers significantly enhanced the predictive capability of the model. Future external validation of our model is required prior to implementation in a clinical environment.

Abbreviations

AUC	Area under curve
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
CVEs	Cardiovascular disease events
DM	Diabetes mellitus
eGRF	Estimated glomerular filtration rate
HbA1c	Haemoglobin A1c
IQR	Interquartile range
LASSO	Least absolute shrinkage and selection operator
LGBM	Light gradient boosting machine
LR	Logistic regression
METS	Metabolic score for insulin resistance
ML	Machine learning
RF	Randomforest
ROC	Receiver operating characteristic curve
SHAP	Shapley Additive exPlanations
SVC	Support vector classification
SVM	Support Vector Machine
TyG	Triglyceride glucose
UAE	Urine albumin excretion
XGBM	EXtreme gradient boosting machine

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02615-w.

Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4: Fig. 1. Correlation of each two variables presented with spearman correlation. SBP, systolic blood pressure; HR, heart rate; TyG, triglyceride glucose; ALT, alanine transaminase; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; CRP, C-reactive protein; HGB, haemoglobin; WBC, white blood cell; FIB-4, fibrosis 4 score; CAD, coronary artery disease; PAD, peripheral artery disease

Supplementary Material 5: Fig. 2. Feature importance determined with LBGM ML model. eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; TyG, triglyceride glucose; HbA1c, haemoglobin A1c; HTN, hypertension; CAD, coronary artery disease; HF, heart failure. Stroke means history of stroke

Supplementary Material 6: Fig. 3. The interaction and dependence of the features based in SHAP value. **A**–**C** Three representative feature (eGFR, age, and TyG) and their interaction, eGFR with TyG (**A**), age with eGFR (**B**), and TyG with age (**C**); **D** Seven features and their interaction. eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; TyG, triglyceride glucose; CRP, C-reactive protein; CAD, coronary artery disease

Supplementary Material 7.

Acknowledgements

Not applicable.

Author contributions

H.K., B.H., Y.C., G.L., and K.N. conceived and designed the data analysis; H.K., J.G.,G.L., and K.N. designed the project; O.J., H.K., K.I., M.H., J.P., W.W., and K.N. collected the data. B.H. and Y.C. performed the statistical analysis. O.J., H.K., K.I., Y.L., M.M., and K.N. provided technical input. H.K., Y.L., and M.M. provided methological input. H.K., B.H., Y.C., and O.J. drafted the original manuscript. Y.Z., U.A., J.G., G.L., and K.N. provided senior methodological input. H.K., O.J., U.A., J.G., G.L., and K.N. reviewed and edited the manuscript. K.N. performed funding acquisition. K.N. was the guarantor of the work and supervised the data analysis. All authors read and approved the final manuscript. H.K., B.H., Y.C. contributed equally to this work.

Funding

This research was funded by the Medical University of Silesia, statutory work number BNW-1/020/N/4/K.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Based on the decision of the Bioethics Committee of the Medical University of Silesia in Katowice, the need for ethical approval was waived (decision no. PCN/0022/KB/126/20).

Consent for publication

All authors gave consent for the publication of the article.

Consent to participate

Not applicable.

Competing interests

G.L. is a consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Anthos and Daiichi-Sankyo. No fees are received personally. G.L. is a NIHR Senior Investigator and co-PI of the AFFIRMO project on multimorbidity in AF (grant agreement No 899871), TARGET project on digital twins for personalised management of atrial fibrillation and stroke (grant agreement No 101136244) and ARISTOTELES project on artificial intelligence for management of chronic long term conditions (grant agreement No 101080189), which are all funded by the EU's Horizon Europe Research & Innovation program. U.A. has received investigator-led funding form Proctor & Gamble. U.A. has received honoraria from Viatris, Grünenthal, Eli Lilly, Procter & Gamble, and Sanofi for educational meetings. U.A. has received funding for attendance to an international medical conference from Diiachi Sankyo. U.A. is member of the Royal Society of Medicine's Vascular, Lipid & Metabolic Medicine Section (Unpaid). K.N. received remunerations/fees for activities on behalf of Sanofi Aventis, Eli Lilly, Novo Nordisk, Astra-Zeneca, Boehringer-Ingelheim and received support for attending meetings and/or travel from Sanofi Aventis. H.K. received remunerations/fees for activities on behalf of Sanofi Aventis, Eli Lilly, Novo Nordisk, Astra-Zeneca, Boehringer-Ingelheim and received support for attending meetings and/or travel from Sanofi Aventis. Others declared none conflict of interest.

Author details

[1]Department of Internal Medicine, Diabetology and Nephrology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, 40-055 Katowice, Poland
[2]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart and Chest Hospital, Liverpool, UK
[3]Department of Cardiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[4]Doctoral School, Department of Internal Medicine, Diabetology and Nephrology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[5]Department of Cardiovascular Medicine, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, China
[6]Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy
[7]Department of Eye and Vision Sciences, University of Liverpool, Liverpool, UK
[8]Student's Scientific Association at the Department of Internal Medicine, Diabetology and Nephrology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[9]Department of Medicine, University Hospital Aintree, Liverpool University Hospitals NHS Foundation Trust, Aintree Hospital, Liverpool, UK
[10]Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Received: 20 October 2024 / Accepted: 26 January 2025
Published online: 15 February 2025

References

1. de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and kidney disease: improving global outcomes (KDIGO). Diabetes Care. 2022;45(12):3075–90. https://doi.org/10.2337/dci22-0027.
2. Ruhe J, Nadal J, Barthlein B, Meiselbach H, Schultheiss UT, Kotsis F, et al. Cardiovascular risk due to diabetes mellitus in patients with chronic kidney disease-prospective data from the German chronic kidney disease cohort. Clin Kidney J. 2023;16(11):2032–40. https://doi.org/10.1093/ckj/sfad194.
3. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS, et al. The Framingham predictive instrument in chronic kidney disease. J Am Coll Cardiol. 2007;50(3):217–24. https://doi.org/10.1016/j.jacc.2007.03.037.
4. Ahmad A, Lim LL, Morieri ML, Tam CH, Cheng F, Chikowore T et al. Precision prognostics for cardiovascular disease in Type 2 diabetes: a systematic review and meta-analysis. Commun Med (Lond). 2024;4(1):11. https://doi.org/10.1038/s43856-023-00429-z.
5. Willis M, Asseburg C, Slee A, Nilsson A, Neslusan C. Development and internal validation of a discrete event simulation model of diabetic kidney disease using CREDENCE trial data. Diabetes Ther. 2020;11(11):2657–76. https://doi.org/10.1007/s13300-020-00923-w.
6. Mcmurray JJ, Uno H, Jarolim P, Desai AS, de Zeeuw D, Eckardt KU, et al. Predictors of fatal and nonfatal cardiovascular events in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia: an analysis of the Trial to reduce cardiovascular events with Aranesp (darbepoetin-alfa) therapy (TREAT). Am Heart J. 2011;162(4):748–55. https://doi.org/10.1016/j.ahj.2011.07.016.
7. Bidadkosh A, Lambooy S, Heerspink HJ, Pena MJ, Henning RH, Buikema H, et al. Predictive properties of biomarkers GDF-15, NTproBNP, and hs-TnT for morbidity and mortality in patients with type 2 diabetes with nephropathy. Diabetes Care. 2017;40(6):784–92. https://doi.org/10.2337/dc16-2175.
8. Khera R, Oikonomou EK, Nadkarni GN, Morley JR, Wiens J, Butte AJ, et al. Transforming cardiovascular care with Artificial Intelligence: from discovery to practice: JACC state-of-the-art review. J Am Coll Cardiol. 2024;84(1):97–114. https://doi.org/10.1016/j.jacc.2024.05.003.
9. Helm JM, Swiergosz AM, Haeberle HS, Karnuta JM, Schaffer JL, Krebs VE, et al. Machine learning and Artificial Intelligence: definitions, applications, and future directions. Curr Rev Musculoskelet Med. 2020;13(1):69–76. https://doi.org/10.1007/s12178-020-09600-8.
10. Kokori E, Patel R, Olatunji G, Ukoaka BM, Abraham IC, Ajekiigbe VO et al. Machine learning in predicting heart failure survival: a review of current models and future prospects. Heart Fail Rev. 2024. https://doi.org/10.1007/s10741-024-10474-y.
11. Zhu H, Qiao S, Zhao D, Wang K, Wang B, Niu Y, et al. Machine learning model for cardiovascular disease prediction in patients with chronic kidney disease. Front Endocrinol (Lausanne). 2024;15:1390729. https://doi.org/10.3389/fendo.2024.1390729.
12. Nabrdalik K, Kwiendacz H, Drozdz K, Irlik K, Hendel M, Wijata AM, et al. Machine learning predicts cardiovascular events in patients with diabetes: the Silesia Diabetes-Heart Project. Curr Probl Cardiol. 2023;48(7):101694. https://doi.org/10.1016/j.cpcardiol.2023.101694.
13. Kwiendacz H, Wijata AM, Nalepa J, Piasnik J, Kulpa J, Herba M et al. Machine learning profiles of cardiovascular risk in patients with diabetes mellitus: the Silesia Diabetes-Heart Project. Cardiovasc Diabetol. 2023;22(1):218. https://doi.org/10.1186/s12933-023-01938-w.
14. Forne C, Cambray S, Bermudez-Lopez M, Fernandez E, Bozic M, Valdivielso JM. Machine learning analysis of serum biomarkers for cardiovascular risk assessment in chronic kidney disease. Clin Kidney J. 2020;13(4):631–39. https://doi.org/10.1093/ckj/sfz094.
15. Degenhardt F, Seifert S, Szymczak S. Evaluation of variable selection methods for random forests and omics data sets. Brief Bioinform. 2019;20(2):492–503. https://doi.org/10.1093/bib/bbx124.
16. Kamkar I, Gupta SK, Phung D, Venkatesh S. Stabilizing l1-norm prediction models by supervised feature grouping. J Biomed Inf. 2016;59:149–68. https://doi.org/10.1016/j.jbi.2015.11.012.
17. Aas K, Jullum M, Løland A. Explaining individual predictions when features are dependent: more accurate approximations to Shapley values. Artif Intell. 2021;298:103502.
18. Ren J, Liu D, Li G, Duan J, Dong J, Liu Z. Prediction and risk stratification of cardiovascular disease in diabetic kidney disease patients. Front Cardiovasc Med. 2022;9:923549. https://doi.org/10.3389/fcvm.2022.923549.
19. Binson VA, Thomas S, Subramoniam M, Arun J, Naveen S, Madhu S. A review of machine learning algorithms for biomedical applications. Ann Biomed Eng. 2024;52(5):1159–83. https://doi.org/10.1007/s10439-024-03459-3.

20. Uddin S, Khan A, Hossain ME, Moni MA. Comparing different supervised machine learning algorithms for disease prediction. BMC Med Inf Decis Mak. 2019;19(1):281. https://doi.org/10.1186/s12911-019-1004-8.
21. Rufo DD, Debelee TG, Ibenthal A, Negera WG. Diagnosis of diabetes mellitus using gradient boosting machine (LightGBM). Diagnostics (Basel). 2021;11(9). https://doi.org/10.3390/diagnostics11091714.
22. Yu KH, Beam AL, Kohane IS. Artificial intelligence in healthcare. Nat Biomed Eng. 2018;2(10):719– 31. https://doi.org/10.1038/s41551-018-0305-z.
23. Ali S, Akhlaq F, Imran AS, Kastrati Z, Daudpota SM, Moosa M. The enlightening role of explainable artificial intelligence in medical & healthcare domains: a systematic literature review. Comput Biol Med. 2023;166:107555. https://doi.org/10.1016/j.compbiomed.2023.107555.
24. Dharmarathne G, Bogahawaththa M, Mcafee M, Rathnayake U, Meddage D. On the diagnosis of chronic kidney disease using a machine learning-based interface with explainable artificial intelligence. Intell Syst Appl. 2024;22. https://doi.org/10.1016/j.iswa.2024.200397.
25. Dharmarathne G, Bogahawaththa M, Rathnayake U, Meddage D. Integrating explainable machine learning and user-centric model for diagnosing cardiovascular disease: a novel approach. Intell Syst Appl. 2024;23. https://doi.org/10.1016/j.iswa.2024.200428.
26. Dharmarathne G, Jayasinghe T, Bogahawaththa M, Meddage D, Rathnayake U. A novel machine learning approach for diagnosing diabetes with a self-explainable interface. Healthc Anal. 2024;5. https://doi.org/10.1016/j.health.2024.100301.
27. Filho M. How To Get Feature Importance In LightGBM (Python example). https://forecastegy.com/posts/feature-importance-lightgbm-python-example/ 2023.
28. Bhatt N. Shap feature importance deep dive. https://medium.com/@bneeraj026/shap-feature-importance-deep-dive-1b96a9d43d082023.
29. Chen YY, Lin YJ, Chong E, Chen PC, Chao TF, Chen SA, et al. The impact of diabetes mellitus and corresponding HbA1c levels on the future risks of cardiovascular disease and mortality: a representative cohort study in Taiwan. PLoS ONE. 2015;10(4):e123116. https://doi.org/10.1371/journal.pone.0123116.
30. Lee AK, Warren B, Lee CJ, Mcevoy JW, Matsushita K, Huang ES, et al. The association of severe hypoglycemia with incident cardiovascular events and mortality in adults with type 2 diabetes. Diabetes Care. 2018;41(1):104–11. https://doi.org/10.2337/dc17-1669.
31. Wang Y, Hou R, Ni B, Jiang Y, Zhang Y. Development and validation of a prediction model based on machine learning algorithms for predicting the risk of heart failure in middle-aged and older US people with prediabetes or diabetes. Clin Cardiol. 2023;46(10):1234–43. https://doi.org/10.1002/clc.24104.
32. Abegaz TM, Baljoon A, Kilanko O, Sherbeny F, Ali AA. Machine learning algorithms to predict major adverse cardiovascular events in patients with diabetes. Comput Biol Med. 2023;164:107289. https://doi.org/10.1016/j.compbiomed.2023.107289.
33. Wang Y, Shi Y, Xiao T, Bi X, Huo Q, Wang S, et al. A Klotho-based machine learning model for prediction of both kidney and cardiovascular outcomes in chronic kidney disease. Kidney Dis (Basel). 2024;10(3):200–12. https://doi.org/10.1159/000538510.
34. Jaeger BC, Sakhuja S, Hardy ST, Akinyelure OP, Bundy JD, Muntner P, et al. Predicted cardiovascular risk for United States adults with diabetes, chronic kidney disease, and at least 65 years of age. J Hypertens. 2022;40(1):94–101. https://doi.org/10.1097/HJH.0000000000002982.
35. Ramezankhani A, Azizi F, Hadaegh F. Association between estimated glomerular filtration rate slope and cardiovascular disease among individuals with and without diabetes: a prospective cohort study. Cardiovasc Diabetol. 2023;22(1):270. https://doi.org/10.1186/s12933-023-02008-x.
36. Tao LC, Xu JN, Wang TT, Hua F, Li JJ. Triglyceride-glucose index as a marker in cardiovascular diseases: landscape and limitations. Cardiovasc Diabetol. 2022;21(1):68. https://doi.org/10.1186/s12933-022-01511-x.
37. Chen J, Wu K, Lin Y, Huang M, Xie S. Association of triglyceride glucose index with all-cause and cardiovascular mortality in the general population. Cardiovasc Diabetol. 2023;22(1):320. https://doi.org/10.1186/s12933-023-02054-5.
38. Tai S, Fu L, Zhang N, Yang R, Zhou Y, Xing Z, et al. Association of the cumulative triglyceride-glucose index with major adverse cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol. 2022;21(1):161. https://doi.org/10.1186/s12933-022-01599-1.
39. Quiroga B, Munoz RP, Sanchez HA, Ortiz A, Valdivieso JM, Carrero JJ. Triglycerides-glucose index and the risk of cardiovascular events in persons with non-diabetic chronic kidney disease. Clin Kidney J. 2022;15(9):1705–12. https://doi.org/10.1093/ckj/sfac073.
40. Ponce-Bobadilla AV, Schmitt V, Maier CS, Mensing S, Stodtmann S. Practical guide to SHAP analysis: explaining supervised machine learning model predictions in drug development. Clin Transl Sci. 2024;17(11):e70056. https://doi.org/10.1111/cts.70056.
41. Nabrdalik K, Irlik K, Meng Y, Kwiendacz H, Piasnik J, Hendel M, et al. Artificial intelligence-based classification of cardiac autonomic neuropathy from retinal fundus images in patients with diabetes: the Silesia Diabetes Heart Study. Cardiovasc Diabetol. 2024;23(1):296. https://doi.org/10.1186/s12933-024-02367-z.
42. Chowdhury M, Nevitt S, Eleftheriadou A, Kanagala P, Esa H, Cuthbertson DJ, et al. Cardiac autonomic neuropathy and risk of cardiovascular disease and mortality in type 1 and type 2 diabetes: a meta-analysis. BMJ Open Diabetes Res Care. 2021;9(2). https://doi.org/10.1136/bmjdrc-2021-002480.

Publisher's note