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## Research article

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## RESEARCH

# Research on Early Warning of Renal Damage in Hypertensive Patients Based on Stacking Strategy

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## Abstract

**Background:** Among the problems caused by hypertension, the early renal damage is often ignored. It can not be diagnosed until the condition is serious and irreversible damage occurs. So we decide to screen and explore related risk factors for hypertensive patients with early renal damage, and establish early-warning model of renal damage based on the data-mining method to achieve early diagnosis for hypertensive patients with renal damage.

**Methods:** With the aid of electronic information management system for hypertensive specialist out-patient, we collected 513 cases of original untreated hypertensive patients, and recorded their demographic data, ambulatory blood pressure parameters, blood routine index, and blood biochemical index to establish the clinical database, then we screen risk factors for early renal damage through feature engineering, and use Random Forest, Extra-Trees, and XGBoost to build an early-warning model, respectively. Finally, we build a new model by model fusion based on Stacking strategy. We use cross validation to evaluate the stability and reliability of each mode to determine the best risk assessment model.

**Results:** According to the degree of importance, the descending order of features selected by feature engineering is the drop rate of systolic blood pressure at night, the red blood cell distribution width, blood pressure circadian rhythm, the average diastolic blood pressure at daytime, body surface area, smoking, age, and HDL. Among the early-warning models of renal damage without model fusion, XGBoost has the best effect, the average accuracy of 5-fold cross validation is 0.90457. And the average accuracy of the two-dimensional fusion model based on Stacking strategy is 0.91428, which is greatly improved.

**Conclusions:** Through feature engineering and risk factor analysis, we select the drop rate of systolic blood pressure at night, the red blood cell distribution width, blood pressure circadian rhythm, and the average diastolic blood pressure at daytime as early-warning factors of early renal damage in patients with hypertension. On this basis, the two-dimensional fusion model based on Stacking strategy has a better effect than the single model, which can be used for risk assessment of early renal damage in hypertensive patients.

**Keywords:** Hypertension; Renal Damage; Risk Assessment; Data Mining; Feature Engineering; Stacking Model

## Background

According to 2020 international society of hypertension global hypertension practice guidelines, hypertension is related to cerebrovascular disease and ischemic heart disease, and is also a major risk factor for the incidence and death due to chronic kidney disease [1]. Hypertension can affect the function of organs in the

whole body, and the kidney is most easily affected. The number of uremic patients caused by hypertension in China reaches 1.5 million every year [2]. Furthermore, among the problems caused by hypertension, the early renal damage is often ignored because of unclear symptoms. As time goes by, the typical symptoms and signs of chronic renal failure gradually appear. It can not be diagnosed until the condition is serious and irreversible damage occurs. How to identify such patients early and make correct intervention is a serious challenge for clinicians, because it is not only related to delaying the progress of renal damage and reducing medical

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expenses, but also closely related to the prognosis of patients. Therefore, we need to pay great attention to the early renal damage in hypertensive patients.

In clinical practice, it is hard to realize the early diagnosis of the high-risk population of hypertensive renal damage and guide different patients to choose the most suitable scheme to receive treatment in time. Because of few or no symptoms in the early stage of chronic kidney disease (CKD), most patients with renal damage fail to get timely diagnosis. Many hypertensive patients that look healthy may have developed CKD, and current methods fail to fully diagnose these patients. We intend to establish an early-warning model based on data mining to evaluate the risk of early renal damage by integrating the relevant factors including cardiovascular risk factors, blood pressure parameters, blood biochemical indicators, and related biomarkers [3, 4, 5]. Then we can use the model to identify the high-risk patients early to make a definite diagnosis and give timely treatment. And we should explore an effective management mode of early hypertensive renal damage to control the risk factors of this population and reduce the incidence rate and harm of CKD.

## Methods

In order to achieve the early diagnosis of high-risk population with hypertensive renal damage, we will screen the early-warning risk factors of early renal damage by feature engineering [6]. Based on these risk factors, we use data mining approach to establish an early-warning model of renal damage, which fuses three machine learning sub-models which are XGBoost, Random Forest and Extra-Trees by Stacking strategy [7, 8, 9]. The specific steps are as follows. (1) data preparation; (2) exploratory data analysis; (3) feature construction; (4) feature selection; (5) model optimization and fusion; (6) model evaluation. The specific process of model construction is shown in the Figure 1.

### Data preparation

From November 2011 to May 2013, Beijing Anzhen Hospital of Capital Medical University (Beijing Institute of Heart Lung and Blood Vessel Diseases), Third Xiangya Hospital of Central South University (Hunan Hypertension Research Center), and Chenzhou No.1 People's Hospital of Hunan Province (Translational Medicine Institute of University of South China) received 513 patients without complications who were initially diagnosed hypertension and aged between 35 and 64, including 319 males and 194 females. None of the patients had ever taken any antihypertensive

drugs before their visit. According to their albumin-to-creatinine ratio (ACR) levels, the patients are divided into two groups: positive group (30-300mg / g), which is the early renal damage group, and control group (<30mg / g), which is the normal renal function group. The number of patients in the two groups is 191 and 322, respectively.

In the comparison of the data of the two groups of patients, the levels of fasting blood-glucose (FBG), triglyceride (TG), uric acid (UA), and red cell distribution width (RDW) in the positive group are greatly higher than those in the control group, and the differences between the two groups are statistically significant ( $P < 0.05$ ); The levels of sex ratio, body mass index (BMI), high density lipoprotein (HDL), low density lipoprotein (LDL), blood urea nitrogen (BUN), and serum creatinine (Scr) are similar, and the differences are not statistically significant ( $P > 0.05$ ). See Table 1.

### Exploratory data analysis

Exploratory data analysis is a data analysis method [10, 11] to explore data structures by means of mapping, tabulation, equation fitting, calculation of characteristic quantity, and other means for existing data under the minimum prior assumption, specifically including: statistical characteristics of data fields, missing situation, distribution, correlation, etc., so as to facilitate the later feature engineering and model construction.

We conduct exploratory data analysis on the collected hypertension patient data. First, we count the number, missing values, mean, standard deviation, median, minimum, maximum, 25% quantile, 50% quantile, and 75% quantile of individual attributes. Then according to the statistical results, we select the appropriate attributes for the statistics of the distribution. Finally, we count the P value of a single attribute and ACR, and count the correlation coefficient between multiple attributes. The relevant processing results are shown in table 2, table 3, table 4, and table 5.

For the features with more missing values (>40%) and unimportant, they can be deleted. Features with less missing values can be filled. We can use statistics to fill in, such as mean, median, mode. For continuous values, it is recommended to use median, which can exclude the influence of some outliers that are large or small. For discrete values, we can use mode to fill in.

### Feature construction

Based on the information obtained from data analysis and combined with the understanding of hypertensive renal damage, we analyze and construct the following features.

(1) Personal information features: height, weight, age, sex, BMI, smoking or not, and body surface area(BSA).

(2) Ambulatory blood pressure features: 24-hour average SBP, 24-hour average DBP, 24-hour average heart rate, day average SBP, day average DBP, day average heart rate, night SBP drop rate, night DBP drop rate, blood pressure circadian rhythm, night average DBP, and night average SBP.

(3) Blood biochemical and routine features: HDL, TG, FBG, UA, LDL, RDW, and BUN.

#### Feature selection

Feature selection is also called feature subset selection or attribute selection. It refers to selecting a subset of features from all features to make the constructed model best [12]. In the application of data mining, the number of features is usually large, among which there may be uncorrelated features, and there may be interdependence between the features. It is easy to increase the model training time and cause curse of dimensionality [13]. In addition, the model will also become complicated, and its generalization ability will decline.

For feature selection, we use the following methods:

(1) Using the variance selection method, we calculated the variance of each feature, and then eliminated the feature with variance less than the threshold. (2) Using the correlation coefficient method, we calculated the correlation coefficient and P value between each feature and the target value. (3) Using the variance inflation factor to determine the correlation between variables to perform multicollinearity detection. (4) Using random forest as the base model to train to get the importance of different features for selection.

#### Model optimization and fusion

We use the K-Fold function for cross-validation in the scikit-learn to divide the data into 5 sets of train set and test set to perform 5-fold cross-validation [14], which can effectively avoid the risk of overfitting caused by limited data volume. The data distribution in the train set and test set is similar to the distribution of all data.

In order to determine the best prediction model, we use Random Forest, Extra-Trees and XGBoost to train the data. During model training, we use grid search to adjust and optimize model parameters. Grid search is a model parameter optimization method [15], whose essence is an exhaustive method. For each parameter, we select a small finite set to explore and carry out the Cartesian product on these parameters to obtain several sets of parameters. Then, grid search uses each set of parameters to train the model, and picks out the best set of parameters [16].

After the above model training is completed, we use the Stacking method to integrate above models to build a new model to improve the prediction effect. The Stacking model fusion strategy is based on the idea of K-fold cross-validation, whose essence is a hierarchical model integration framework to stack the learning ability of different models for different features. However, as the number of layers increases, there is a risk of overfitting. Therefore, we usually use a two-layer model to reduce the number of data repeat training. The first layer model is composed of several base learners whose input is the original train set. And the second layer model uses the output of the first layer model as the train set to retrain. The structure of Stacking model fusion strategy is shown in Figure 2.

We use the two-dimensional fusion model based on the stacking strategy. The first layer model uses the combination of random forest, extra trees and XGBoost as the base learner to train the data, and the second layer model uses XGBoost to train the output of the first layer model.

## Result

### Risk factors

The steps of feature selection are shown in the Figure 3. After feature selection, we select 8 features. According to the order of importance from high to low, they are as follows: drop rate of systolic blood pressure at night(night SBP drop rate), red blood cell distribution width(RDW), blood pressure circadian rhythm, average diastolic blood pressure at daytime(day average DBP), body surface area(BSA), smoking, age and HDL. The importance of features is shown in the Table 6.

### Model

The accuracy, recall, and F1 score results of 5-fold cross validation for each model are shown in the Table 7. In single model training, the effect of Random Forest and XGBoost is similar. XGBoost has the highest accuracy, while Random Forest has the highest recall rate and F1 score. Compared with Random Forest, Extra-Trees, and XGBoost, the two-dimensional fusion model based on Stacking method has the highest accuracy, recall rate and F1 value. The first layer of fusion model is consist of XGBoost, Extra-Trees and RF. And the second layer of fusion model is XGBoost.

The accuracy of each fold in 5-fold cross validation for each model is shown in Figure 4. The recall of each fold in 5-fold cross validation for each model is shown in Figure 5. The F1 score of each fold in 5-fold cross validation for each model is shown in Figure 6. From

the training results of each fold, we can find that the training effect of the fusion model based on Stacking method in each fold is in the top two. It shows that the fusion model based on Stacking method integrates the learning ability of different models for different features to improve prediction effect on all data.

## Discussion

### Risk factor analysis

In the screening of CKD patients and the monitoring of renal function in the treatment, the main clinical index is serum creatinine. But, serum creatinine assessment is not sensitive to the detection of early subclinical changes and the prediction of renal function decline after treatment. In the preclinical stage of CKD, we need new monitoring indicators to evaluate such patients. Early renal damage can be judged by microalbuminuria and glomerular filtration rate (GFR). However, the role of urinary microalbumin has not been deemed significant due to the measurement errors. GFR is affected by many factors. Even though nuclear medicine method measurement is a gold standard, it is seldom carried out due to the complexity of cost and operation. The estimated GFR can not reflect the real renal function because the formula is complicated and the results of different formulas are quite different. This part of the study aims to understand the early renal damage of untreated hypertension patients, screen the relevant risk factors, find out specific high-risk factors, and provide quantitative indicators (early warning signals) for early renal damage hypertension patients and cardiovascular clinicians, so as to better prevent the progress of CKD.

### Abnormal blood pressure indexes

The results of comparison between the two groups show that the patients in the early renal damage hypertension group are older, their HDL is lower, their BSA is lower, and each blood pressure index is higher than that in the control group, especially the nighttime blood pressure level and blood pressure variability. Further analysis shows that the incidence of abnormal blood pressure rhythm in the two groups is quite different. In the early renal damage group, the proportion of non-dipper type, reverse-dipper type and deep dipper type account for 75.9%, 14.1% and 3.1%, respectively, while the normal rhythm is less than 10%. In contrast, 72.4% of the patients in the control group have normal blood pressure rhythm. The analysis of blood pressure circadian rhythm indicates that the difference in the drop rate of nighttime blood pressure between the two groups is statistically significant, and the drop of nighttime blood pressure is weakened in the early renal damage group.

Cheng Dong et al [17] found that the drop of blood pressure at night was an important predictor of renal damage in hypertensive patients. Ningling S et al. [18] studied the albuminuria and blood pressure level of hypertension patients in five different regions in China, and found that poor blood pressure control was an important factor for the occurrence of proteinuria. Effective control of blood pressure had important significance in reducing proteinuria, improving endothelial function and renal protection. Our study finds that SBP, DBP and PP(clinic, 24-hour, day, night) in the ACR positive group are higher than those in the control group ( $P < 0.05$ ) to indicate that the higher the blood pressure level, the higher the incidence of ACR. In addition, our study also concludes that the drop rate of nighttime systolic blood pressure and the average diastolic blood pressure in the daytime are risk factors for the occurrence of ACR, and also shows that the control of blood pressure level is of great significance for the patients with hypertension.

### Abnormal blood pressure rhythm

People's blood pressure is higher in the day and lower in the night. That is to say, the blood pressure drops during sleep at night and is the lowest in the early morning; the blood pressure starts to rise in the early morning and then presents the first peak. During sleep, sympathetic activity, cardiac output, and blood pressure decrease in normal people and patients with arytoid rhythm hypertension. Huijuan K et al. [19] found that compared to patients with dipper hypertension, patients with non-dipper and anti-dipper hypertension were closely related to early renal damage indicators. It indicated that there was a close relationship between the abnormal circadian rhythm of blood pressure and early renal damage. Zeming K et al [20] found that the abnormal blood pressure circadian rhythm was the important factor causing the early-stage renal damage, reverse-dipper make early-stage renal damage was more significant. Nighttime systolic blood pressure levels and blood pressure circadian rhythm had important clinical significance for early-stage renal damage in patients with hypertension.

The results of this study suggest that the ambulatory blood pressure level of patients with early renal damage of hypertension increases with the increase of urinary microalbumin, which is manifested by the increase of nighttime blood pressure, especially the increase of nighttime diastolic blood pressure. The study also finds that the early renal damage of hypertension is often accompanied by the abnormal blood pressure circadian rhythm, and it has existed in the hypertensive patients without microalbuminuria.

In comparison with the patients with dipper and non-dipper rhythm, the patients with anti-dipper rhythm have higher ACR, night SBP, night DBP and night PP, while the decrease of eGFR is more obvious. It suggests that anti-dipper rhythm plays a relevant and independent role in the occurrence and development of early renal damage in hypertension, regardless of whether the clinic blood pressure level and dynamic blood pressure level are the same. In addition, nighttime blood pressure level and circadian rhythm are positively correlated with ACR, but not with eGFR. It suggests that the anti-dipper blood pressure circadian rhythm is independently correlated with the occurrence of microalbuminuria in patients with hypertension. Our study finds that all patients in the anti-dipper rhythm group have early renal damage, which may be due to small sample size or biased selection, but it is enough to show that the early renal damage in the anti-dipper rhythm group is more serious. In the future, we need larger samples and more evidence to confirm the causal relationship between the anti-dipper rhythm and early hypertensive renal damage.

#### *Red blood cell distribution width*

A series of studies confirm the correlation between RDW (Red cell Distribution Width) and hypertension: Tanindi et al. [21] found that hypertensive patients had higher RDW levels and higher systolic and diastolic blood pressure than prehypertensive patients; Perlstein et al. also found that the level of systolic blood pressure and the proportion of hypertensive patients were significantly increased in people with higher RDW [22]; Formal et al. found that RDW is closely related to the delay in the reduction of the nighttime blood pressure in hypertensive patients, which is an independent predictor of nighttime non-dipper blood pressure [23]. Correlation between RDW and renal function has also been reported: Ujszaszi A et al. [24] observed that RDW was independently associated with decreased renal function in renal transplant patients, and considered it as a potential new auxiliary parameter for clinical evaluation for patients with chronic kidney disease. Recently, Solak et al. found that RDW was significantly increased in patients with CKD from stage 1 to stage 5, which was closely related to endothelial dysfunction in patients with chronic kidney disease [25]. However, the above studies are limited to the CKD population, and their results may be affected by drug and disease progression.

This study finds that RDW is associated with early renal damage of hypertensive patients, and the ACR

ratio also tends to increase as RDW increases. Combined with the data in this group, hypertensive patients have different degrees of early renal damage. RDW is a sensitive indicator for the diagnosis of early renal damage of hypertensive patients, and **RDW is a common item of routine blood examination**. The method is convenient, fast, and inexpensive. Of course, RDW, as an indicator of risk assessment of early renal damage in hypertensive patients, still needs evidence support from prospective studies in the future.

#### Model Analysis

When we use Stacking method for model fusion, the corresponding results may be different when the model combination of each layer is different. In order to determine the best combination of models, the first layer model uses the random combination of Random Forest, Extra-Trees and XGBoost as the basic learner, and the second layer uses XGBoost which has the highest accuracy of single model as the classifier. Then, we carry out 5-fold cross validation on the data. Through comparison, we can find that the two-dimensional fusion model based on Random Forest, Extra-Trees and XGBoost is the best. The results of 5-fold cross validation for each model combination is shown in the Table 8.

#### Limitations

There are some limitations in current research. In the aspect of screening risk factors of renal damage in hypertension, due to the inherent limitations of case-control study, to further clarify the relationship between the above risk factors and early renal damage in hypertensive patients, it needs to be further confirmed by more centers, larger samples and prospective studies. In establishing early warning model of renal damage, small sample is a serious limitation, which will affect the accuracy and generalization ability of the model. However, the small sample and data imbalance are common in clinical research. How to apply the model to the clinical research still needs further exploration.

In order to overcome the limitations of this study. We should collect more data about hypertensive patients with early renal damage to validate and optimize the model. And we may solve small sample limitation by few-shot learning. In addition, we could fuse other models with better effect to get better result [26].

#### Conclusion

This study mainly carries out the application research of data mining combined with clinical routine

items in early warning of renal damage in hypertensive patients. We then use feature engineering and risk factor analysis to screen for risk factors such as the drop rate of in systolic blood pressure at night, red blood cell distribution width, blood pressure circadian rhythm, and the average diastolic blood pressure at daytime as early renal damage's warning sign. On this basis, the early-warning model of early kidney damage constructed by Stacking model fusion strategy has a better effect than the single model. This model can not only be used for the auxiliary diagnosis of renal damage in hypertensive patients, but has important significance for the screening of such high-risk populations. In the future, we can try to fuse the better model and test its prediction effect. At the same time, the methods and ideas of this research can also provide new methodological references for similar early-warning research and evaluation.

#### Abbreviations

BMI: Body Mass Index;  
 BSA: body surface area;  
 FBG: Fasting Blood-Glucose;  
 2hPBG: 2h Postprandial Blood Glucose;  
 TG: Triglyceride;  
 HDL-C: High Density Lipoprotein Cholesterol;  
 LDL-C: Low Density Lipoprotein Cholesterol;  
 BUN: Blood Urea Nitrogen;  
 Scr: Serum creatinine;  
 UA: Uric Acid;  
 eGFR: estimated Glomerular Filtration Rate;  
 ACR: Albumin-to-creatinine Ratio;  
 hs-CRP: high-sensitivity C-Reactive Protein;  
 RDW: Red cell Distribution Width;  
 OBPM: Office Blood Pressure Measure;  
 ABPM: Ambulatory Blood Pressure Monitoring;  
 SBP: Systolic Blood Pressure;  
 DBP: Diastolic Blood Pressure;  
 PP: Pulse Pressure;  
 CV: Coefficient of Variability;  
 CKD: Chronic Kidney Disease;  
 LAD: Left Atrium Diameter;  
 LVEDD: Left Ventricular End Diastolic Diameter;  
 LVRWT: Left Ventricular Relative Wall Thickness;  
 MLVRWT: Maximal Left Ventricular Relative Wall Thickness;  
 LVMI: Left Ventricular Mass Index;  
 RF: Random Forest;  
 XGB: XGBoost;  
 ET: Extra Trees

#### Declarations

Ethics approval and consent to participate  
 Not applicable.

Consent for publication  
 Not applicable.

Availability of data and materials  
 The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests  
 None of the authors have a conflict of interest to report.

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#### Author's contributions

HE, ZK and MS designed research. XT and XL collected and analyzed data. QB, HE and ZK designed method. QB and ZK performed the experiments. QB and ZK wrote the manuscript. HE and MS reviewed and edited the manuscript. All of the author(s) have read and approved the final manuscript.

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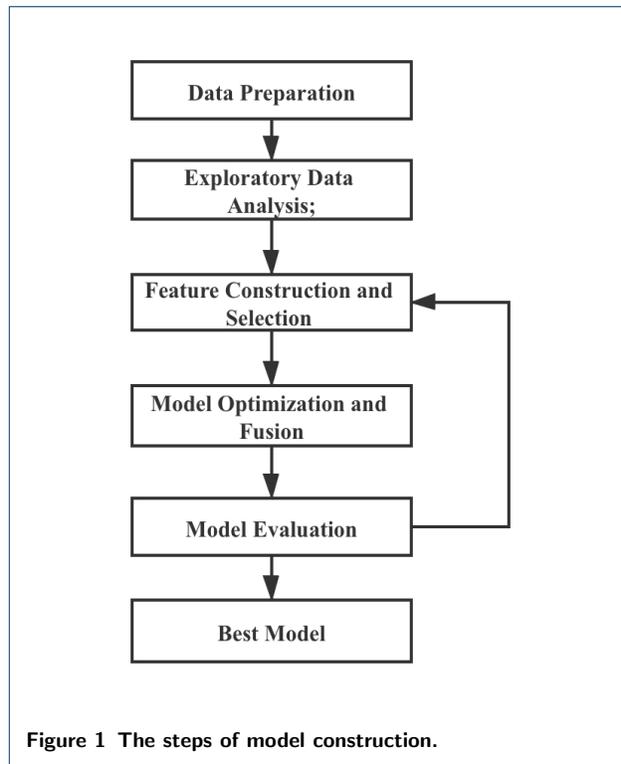
#### References

1. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines[J]. *Journal of Hypertension*, 2020, 75(6):982-1004.
2. Ruilope LM. Simultaneous cardiac and renal damage in a hypertensive population.[J]. *Journal of clinical hypertension (Greenwich, Conn.)*,2009,11(6).
3. Ngufor Che, Van Houten Holly, Caffo Brian S, Shah Nilay D, McCoy Rozalina G. Mixed effect machine learning: A framework for predicting longitudinal change in hemoglobin A1c.[J]. *Journal of biomedical informatics*,2019,89.
4. Lin, Xu, Yun, Hou, Li, Lian, Zheng. A risk prediction model for renal damage in a hypertensive Chinese Han population[J]. *Clinical and Experimental Hypertension*,2019,41(6).
5. Ramezankhani A, Kabir A, Pournik O, Azizi F, Hadaegh F. Classification-based data mining for identification of risk patterns associated with hypertension in Middle Eastern population: A 12-year longitudinal study.[J]. *Medicine*,2016,95(35).
6. Jouhyun J, Peter J. L., Gaurav B, Michael H. Li, Yan F, Alfred J. W. Predicting Glycaemia in Type 1 Diabetes Patients: Experiments in Feature Engineering and Data Imputation. *Journal of Healthcare Informatics Research*.2020.
7. Jiangping C, Jianhua Y, Lin Z, Taixin Z, Mengdi Z. Stacking machine learning model for estimating hourly PM 2.5 in China based on Himawari 8 aerosol optical depth data[J]. *Science of the Total Environment*,2019,697.
8. Amir HZ, Qamar A, Jaime E. Ramirez-Vick, Nasim Nosoudi. Characterizing basal-like triple negative breast cancer using gene expression analysis: A data mining approach[J]. *Expert Systems With Applications*,2020,148.
9. Bian Jiantao, Abdelrahman Samir, Shi Jianlin, Del Fiol Guilherme. Automatic identification of recent high impact clinical articles in PubMed to support clinical decision making using time-agnostic features.[J]. *Journal of biomedical informatics*,2019,89.
10. Samrat Kumar Dey, Md. Mahbubur Rahman, Umme Raihan Siddiqi, Arpita Howlader. Analyzing the Epidemiological Outbreak of COVID-19: A Visual Exploratory Data Analysis (EDA Approach)[J]. *Journal of Medical Virology*,2020(preaccepted).
11. Fotouhi Sara, Asadi Shahrokh, Kattan Michael W. A comprehensive data level analysis for cancer diagnosis on imbalanced data.[J]. *Journal of biomedical informatics*,2019,90.
12. Haiyang L, Zhihai W, Yange S. Stacking model of multi-label classification based on pruning strategies. *Neural Computing and Applications*.2018.
13. Márcio Dias de Lima, Juliana de Oliveira Roque e Lima, Rommel M. Barbosa. Medical data set classification using a new feature selection

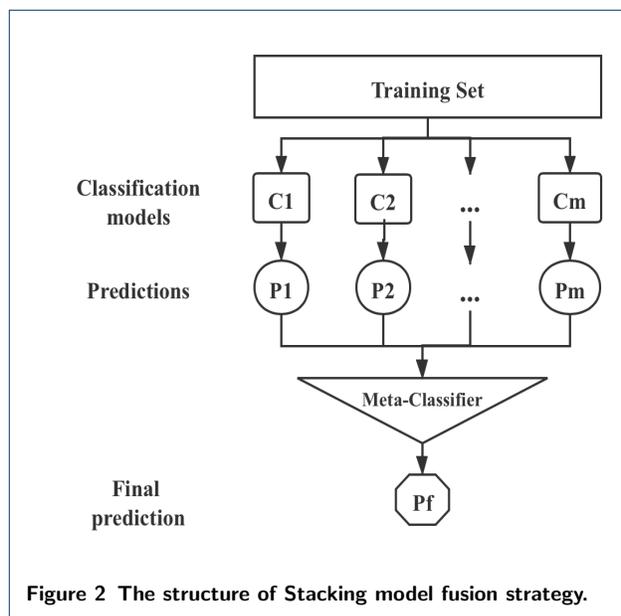
algorithm combined with twin-bounded support vector machine. *Medical & Biological Engineering & Computing*, 2020, Vol.58 (3), pp.519-528.

14. Till Braun, Sotirios Spiliopoulos, Charlotte Veltman, Vera Hergesell, Alexander Passow, Gero Tenderich, Martin Borggreffe, Michael M. Koerner. Detection of myocardial ischemia due to clinically asymptomatic coronary artery stenosis at rest using supervised artificial intelligence-enabled vectorcardiography – A five-fold cross validation of accuracy[J]. *Journal of Electrocardiology*, 2020, 59.
15. Wang Xiashuang, Gong Guanghong, Li Ni, Qiu Shi. Detection Analysis of Epileptic EEG Using a Novel Random Forest Model Combined With Grid Search Optimization. [J]. *Frontiers in human neuroscience*, 2019, 13.
16. Batten Adam, Thorpe Joshua, Piegari Rebecca, Rosland Ann-Marie. A Resampling Based Grid Search Method to Improve Reliability and Robustness of Mixture-Item Response Theory Models of Multimorbidity High-Risk Patients. [J]. *IEEE journal of biomedical and health informatics*, 2019.
17. Cheng Dong, Tang Yi, Li Haiyu, Li Yunpeng, Sang Haiqiang. Nighttime blood pressure decline as a predictor of renal injury in patients with hypertension: a population-based cohort study. [J]. *Aging*, 2019, 11(13).
18. Ningling S, Hongyi W, Dingliang Z, Yuhua L, Shuguang L, Xiaoping C. Association between albuminuria and blood pressure level in patients with essential hypertension. *Chinese Journal of Nephrology*. 2010. 26(10):762-765.
19. Huijuan K, Dengfeng G, Rui M, Xin D, Yongqin L. GW26-e0487 Relationship between Blood Pressure Circadian Rhythm and Early Renal damage in the patients with Primary Hypertension [J]. *Journal of the American College of Cardiology*, 2015, 66(16).
20. Kuang Zemin, Hongjuan Hu, Yu Kong, Yu Zhengqiu, Yuan Hong. GW25-e1517 Blood Pressure Circadian Rhythm Impact on Early-stage Renal Damage in Patients with Hypertension [J]. *Journal of the American College of Cardiology*, 2014, 64(16).
21. Tanindi A, Topal FE, Topal F, Celik B. Red cell distribution width in patients with prehypertension and hypertension *Blood Pros*. 2012. 21(3): 177-81.
22. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. *Archives of internal medicine*. 2009. 169(6): 588-94.
23. Formal M, Wizner B, Cwynar M, et al. Association of red blood cell distribution width, inflammation markers and morphological as well as rheological erythrocyte parameters with target organ damage in hypertension. *Clin Hemorheol Microcirc*. 2013.
24. Ujszaszi A, Molnar MZ, Czira ME, Novak M, Mucsi I. Renal function is independently associated with red cell distribution width in kidney transplant recipients: a potential new auxiliary parameter for the clinical evaluation of patients with chronic kidney disease. *Br J Haematol*. 2013. 161(5): 715-25.
25. Solak Y, Yilmaz MI, Saglam M, et al. Red cell distribution width is independently related to endothelial dysfunction in patients with chronic kidney disease. *Am J Med Sci*. 2014. 347(2): 118-24.
26. Topaz Maxim, Murga Ludmila, Gaddis Katherine M, McDonald Margaret V, Bar-Bachar Ofrit, Goldberg Yoav, Bowles Kathryn H. Mining fall-related information in clinical notes: Comparison of rule-based and novel word embedding-based machine learning approaches. [J]. *Journal of biomedical informatics*, 2019, 90.

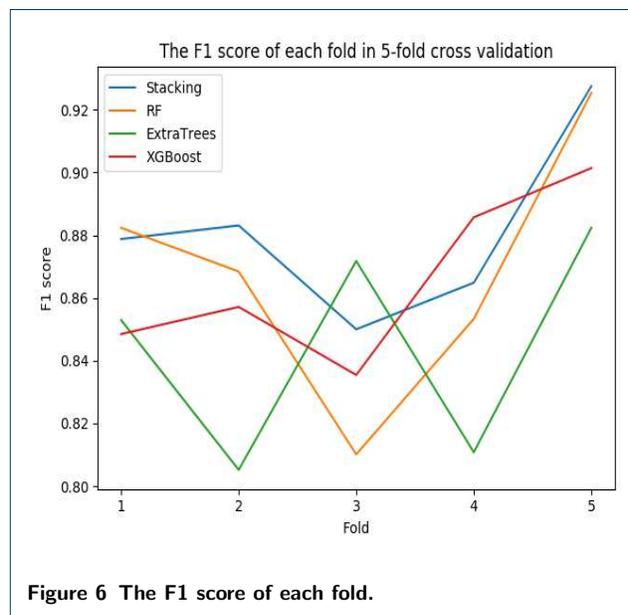
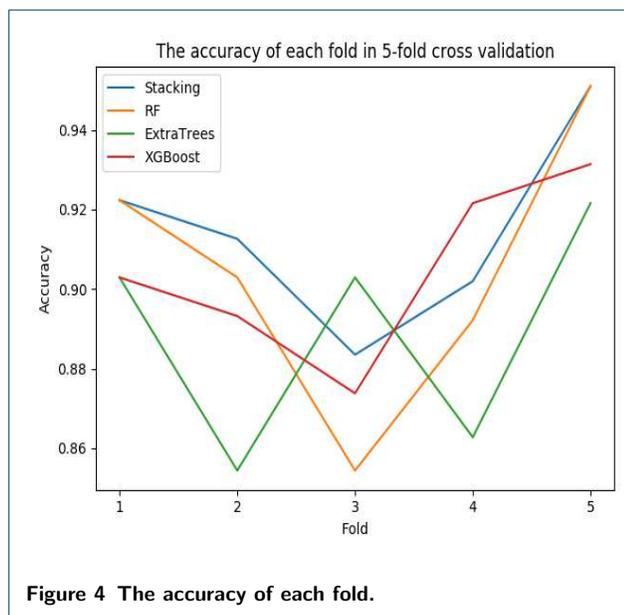
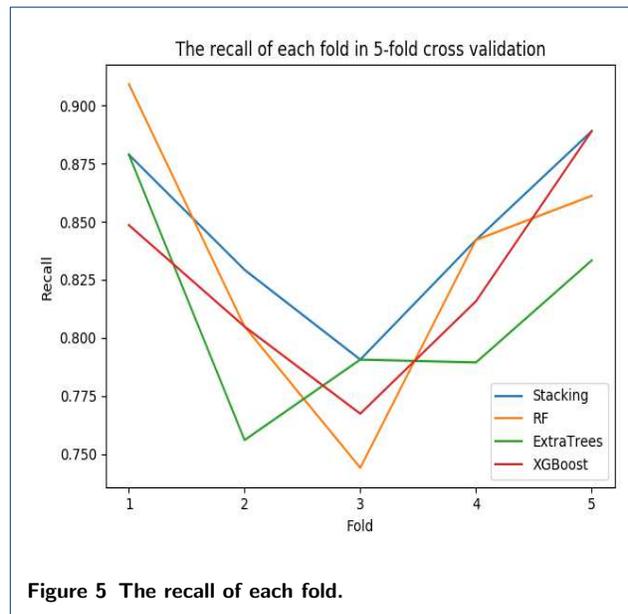
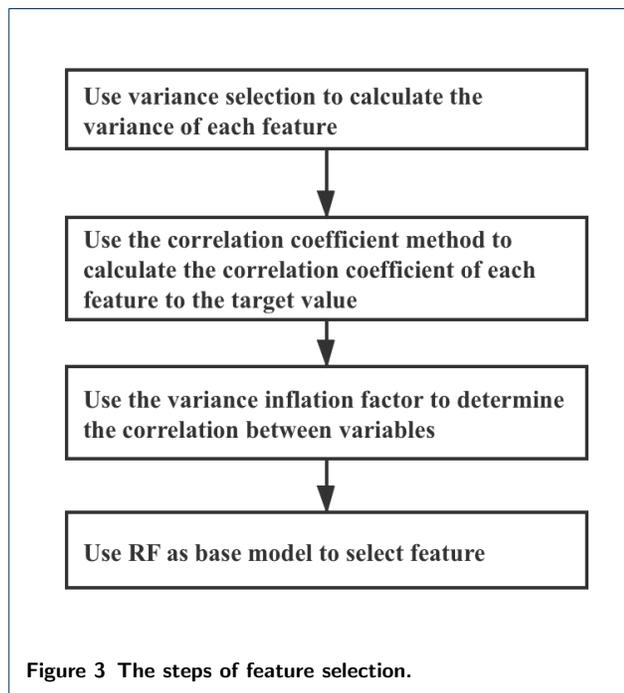
**Additional Files**



**Figure 1** The steps of model construction.



**Figure 2** The structure of Stacking model fusion strategy.



**Table 1** The Comparison of clinical and biochemical data.

Variable	Control group	Positive group	P value
Age	46.37±7.54	47.61±8.14	0.083
Female ratio	36%	40.8%	0.277
BMI(kg/m <sup>2</sup> )	26.03±3.50	25.63±3.26	0.187
HDL(mmol/L)	1.13±0.22	1.10±0.21	0.096
LDL(mmol/L)	3.13±0.87	3.25±0.77	0.136
BUN(mmol/L)	4.80±1.17	4.87±1.07	0.504
Scr(μmol/L)	70.19±13.13	69.63±12.91	0.641
<b>FBG(mmol/L)</b>	<b>5.63±0.67</b>	<b>5.76±0.64</b>	<b>0.027</b>
<b>TG(mmol/L)</b>	<b>1.45~2.12</b>	<b>1.52~2.34</b>	<b>0.047</b>
<b>UA(μmol/L)</b>	<b>337.99±46.87</b>	<b>351.50±49.66</b>	<b>0.002</b>
<b>RDW (%)</b>	<b>12.39±0.63</b>	<b>13.32±0.85</b>	<b>&lt;0.001</b>
ACR(mg/g)	15.87±8.72	74.88±56.42	<0.001

**Table 2** Missing value statistics.

Variable	N	Missing value	%
Hcy	190	323	63.0
2hPBG	219	294	57.3
RVD	313	200	39.0
RVOT	317	196	38.2
WBC	322	191	37.2
RBC	323	190	37.0
Hb	323	190	37.0
Plt	323	190	37.0
A_peak_max	325	188	36.6
EA	325	188	36.6
IVST	330	183	35.7
LVDS	330	183	35.7
LVM	330	183	35.7
LyVII	330	183	35.7
LVH	330	183	35.7
FS	330	183	35.7
E_peak_max	330	183	35.7
LVPWT	331	182	35.5
EF	331	182	35.5
LVEDD	332	181	35.3
SBP_cv_24h	396	117	22.8
DBP_cv_24h	396	117	22.8
Ald	413	100	19.5
PRA	415	98	19.1
Ang2	415	98	19.1
hs-CRP	481	32	6.2
ALT	493	20	3.9
AST	494	19	3.7

**Table 3** Data distribution statistics.

Variable	Distribution	Frequency	Percentage%
ACR	0	322	62.8
	1	191	37.2
BMI	24-28	235	45.8
	<24	149	29.0
	>28	129	25.1
	Dipper	246	48.0
Blood pressure type	Non-dipper	231	45.0
	Reverse-dipper	27	5.3
	Deep-dipper	9	1.8
HFBG	No	369	71.9
	Yes	144	28.1
HTG	No	301	58.7
	Yes	212	41.3
LDL-C	No	410	79.9
	Yes	103	20.1
Proteinuria	No	322	62.8
	Yes	191	37.2
Sex	Male	319	62.2
	Female	194	37.8
Age	35-44	225	43.9
	45-54	182	35.5
	55-64	106	20.7
RDW	<12.2	129	25.1
	12.2-12.7	146	28.5
	12.7-13.2	114	22.2
	>13.2	124	24.2

**Table 4** Multi-collinearity analysis.

Variable	Tolerance	VIF
cDBP	0.333	3.007
<b>24hDBP</b>	<b>0.010</b>	<b>96.394</b>
<b>Day DBP</b>	<b>0.004</b>	<b>262.553</b>
<b>Night SBP drop rate</b>	<b>0.006</b>	<b>176.494</b>
<b>Night DBP drop rate</b>	<b>0.007</b>	<b>150.070</b>
<b>NightDBP</b>	<b>0.003</b>	<b>353.446</b>
SBP_cv_24h	0.581	1.720
DBP_cv_24h	0.396	1.762
cPP	0.311	3.212
<b>24hPP</b>	<b>0.023</b>	<b>42.607</b>
<b>Day PP</b>	<b>0.005</b>	<b>213.029</b>
<b>Night PP</b>	<b>0.004</b>	<b>226.067</b>

**Table 5** Data statistical analysis.

Variable	Average	Standard deviation	Median	Min	Max	25% Quan- tile	50% Quan- tile	75% Quan- tile
ACR	37.84	2.00	24.90	0.00	295.70	12.80	24.90	36.55
age	46.83	0.34	46.00	35.00	64.00	40.00	46.00	53.00
BMI	25.88	0.15	25.56	17.48	40.32	23.53	25.56	28.08
height	168.40	0.38	170.00	145.00	192.00	161.00	170.00	175.00
WT	73.70	0.57	73.00	42.00	138.00	65.00	73.00	81.00
ald	0.16	0.00	0.16	0.01	0.35	0.13	0.16	0.19
Ang2	75.33	1.43	66.92	27.63	229.29	57.89	66.92	84.85
ALT	30.96	1.11	23.00	3.00	222.00	16.00	23.00	36.00
AST	25.35	0.49	22.00	10.00	107.00	19.00	22.00	28.00
BUN	4.82	0.05	4.70	0.84	9.90	4.00	4.70	5.60
Scr	69.98	0.58	71.00	42.00	97.00	59.00	71.00	80.00
TC	5.14	0.04	5.13	3.44	7.89	4.51	5.13	5.72
cPP	52.55	0.48	51.00	25.00	92.00	45.00	51.00	59.00
hs-CRP	2.40	0.22	0.98	0.05	52.15	0.44	0.98	2.17
24hDBP	87.80	0.39	87.00	64.00	122.00	82.00	87.00	93.00
cDBP	99.93	0.39	100.00	69.00	130.00	93.00	100.00	105.50
cv_24h	11.23	0.14	11.00	1.23	20.27	9.33	11.00	13.00
DBP	91.26	0.40	91.00	64.00	125.00	85.00	91.00	97.00
NightDBP	80.75	0.43	80.00	58.00	118.00	74.00	80.00	86.00
Night SBP drop rate	11.45	0.30	11.83	-10.00	30.43	6.82	11.83	16.34
day PP	48.86	0.40	48.00	29.00	81.00	42.00	48.00	54.00
NightSBP	126.86	0.56	126.00	97.00	171.00	118.00	126.00	134.00
Night DBP drop rate	9.44	0.25	9.87	-9.09	25.76	5.93	9.87	13.36
Night PP	46.10	0.40	45.00	27.00	81.00	39.50	45.00	52.00
eGFR	105.02	1.09	102.06	61.63	268.03	88.72	102.06	116.34
FS%	37.51	0.43	37.00	23.00	107.00	33.00	37.00	40.00
FBG	5.68	0.03	5.54	3.75	8.78	5.24	5.54	5.99
Hb	150.01	0.88	151.00	85.00	195.00	140.00	151.00	161.00
Clinic heart rate	78.44	0.41	80.00	52.00	104.00	72.00	80.00	84.00
Day avg heart rate	78.44	0.39	78.00	50.00	109.00	73.00	78.00	84.00
Night avg heart rate	65.08	0.35	65.00	42.00	101.00	60.00	65.00	70.00
24hSBP	135.68	0.49	134.00	111.00	175.00	128.00	134.00	141.50
cSBP	152.47	0.53	150.00	123.00	193.00	143.00	150.00	159.00
24hCV	12.29	0.19	11.63	5.00	26.58	9.49	11.63	14.48
hPP_24h	47.88	0.39	46.00	19.00	79.00	42.00	46.00	53.00
24h avg heart rate	74.28	0.37	74.00	48.00	106.00	69.00	74.00	79.00
DaySBP	140.12	0.49	139.00	113.00	180.00	133.00	139.00	146.00
LVH	0.47	0.03	0.00	0.00	1.00	0.00	0.00	1.00
LVEDD	29.77	0.22	30.00	2.00	44.00	27.00	30.00	32.00
LVEDD	47.29	0.26	47.00	9.70	65.00	45.00	47.00	50.00
LVPWT	9.63	0.10	9.60	6.80	30.00	9.00	9.60	10.00
LVMI	110.57	1.33	108.62	54.41	266.19	94.22	108.62	123.41
RVED	20.30	0.17	20.00	12.00	33.00	18.00	20.00	22.00
RVOTD	28.14	0.36	28.00	16.00	73.00	25.00	28.00	30.00
A_peak_max	75.12	1.09	73.00	26.00	159.00	60.00	73.00	88.00
E_peak_max	79.04	1.13	77.00	30.00	143.00	65.75	77.00	92.00
E/A	1.12	0.02	1.15	0.50	3.39	0.77	1.15	1.36
EF%	65.82	0.34	66.00	33.00	79.00	62.00	66.00	70.00
2hPBG	7.49	0.15	6.99	3.73	16.30	5.90	6.99	8.20
TG	1.85	0.02	1.79	1.00	3.89	1.46	1.79	2.22
LDL-C	3.18	0.04	3.20	1.17	5.92	2.62	3.20	3.74
HDL	1.12	0.01	1.10	0.56	1.91	0.96	1.10	1.26
UA	343.02	2.13	343.80	226.20	471.10	307.25	343.80	376.95
WBC	6.46	0.10	6.23	2.82	16.82	5.29	6.23	7.31
Plt	237.15	2.96	231.00	115.00	476.00	201.00	231.00	267.00
RBC	4.96	0.03	4.97	3.73	8.04	4.63	4.97	5.28
RDW	12.74	0.04	12.70	11.00	16.00	12.20	12.70	13.20
Hcy	15.06	0.83	11.80	5.90	114.20	9.00	11.80	15.83

**Table 6** The importance of features.

Order	Feature name	Importance
1	Night SBP drop rate	0.39149
2	RDW	0.20044
3	Blood pressure circadian rhythm	0.15787
4	Day average DBP	0.07692
5	BSA	0.05067
6	Smoking	0.04294
7	Age	0.04236
8	HDL	0.03732

**Table 7** The results of 5-fold cross validation for each model.

Model	Avg Accuracy	Avg Recall	Avg F1 Score
RF	0.90455	0.83227	0.86792
ExtraTrees	0.88890	0.80968	0.84462
XGBoost	0.90457	0.82510	0.86564
Stacking	0.91428	0.84595	0.88086

**Table 8** The results of 5-fold cross validation for each combination. ET is ExtraTrees, RF is Random Forest, and XGB is XGBoost.

First Layer	Avg Accuracy	Avg Recall	Avg F1 Score
RF	0.89869	0.82599	0.85942
ET	0.89086	0.81607	0.84857
XGB	0.90065	0.82510	0.86072
RF+ET	0.89282	0.82050	0.85103
XGB+RF	0.90457	0.82510	0.86564
XGB+ET	0.90457	0.82510	0.86564
XGB+ET+RF	0.91428	0.84595	0.88086

## Figures

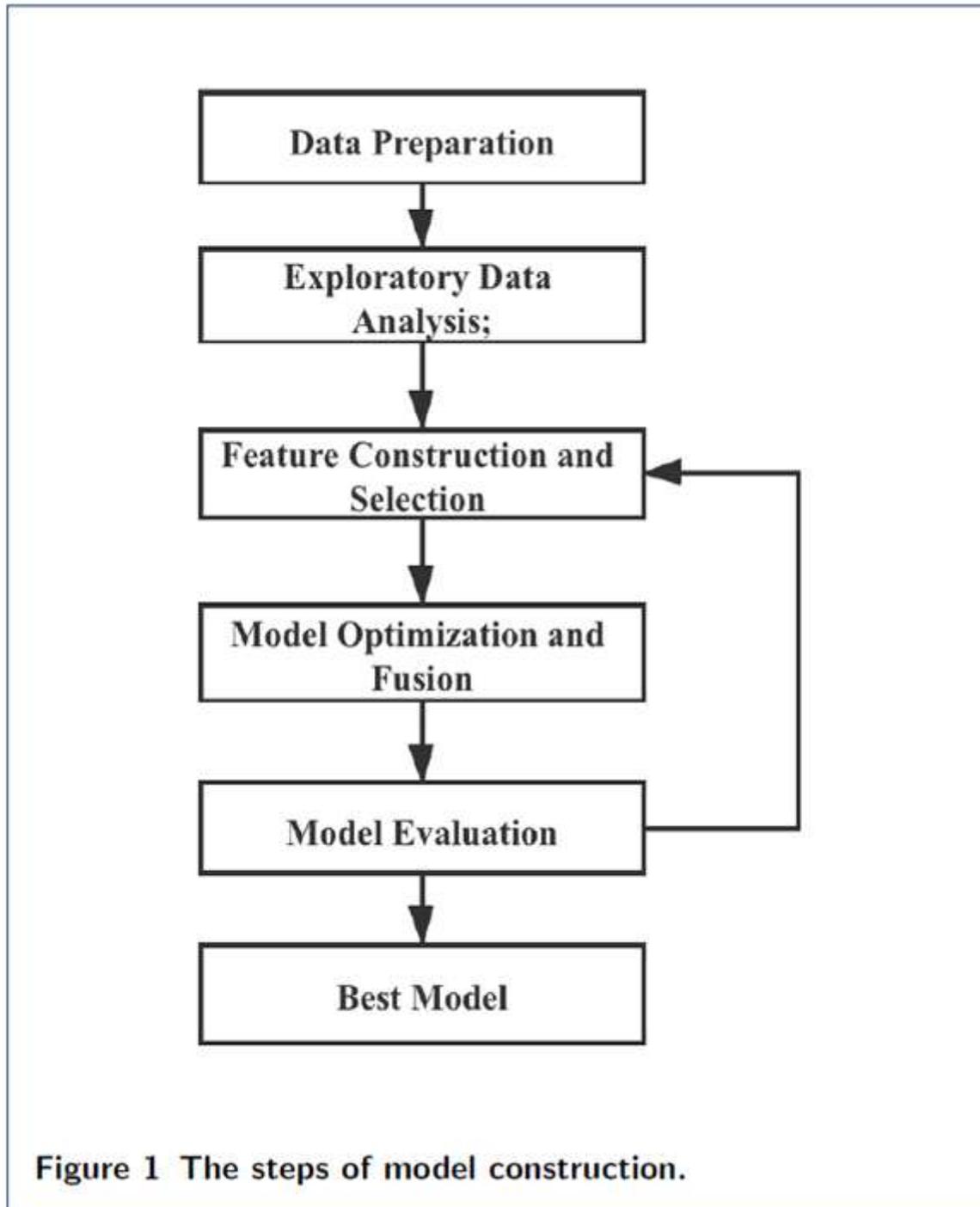


Figure 1

The steps of model construction.

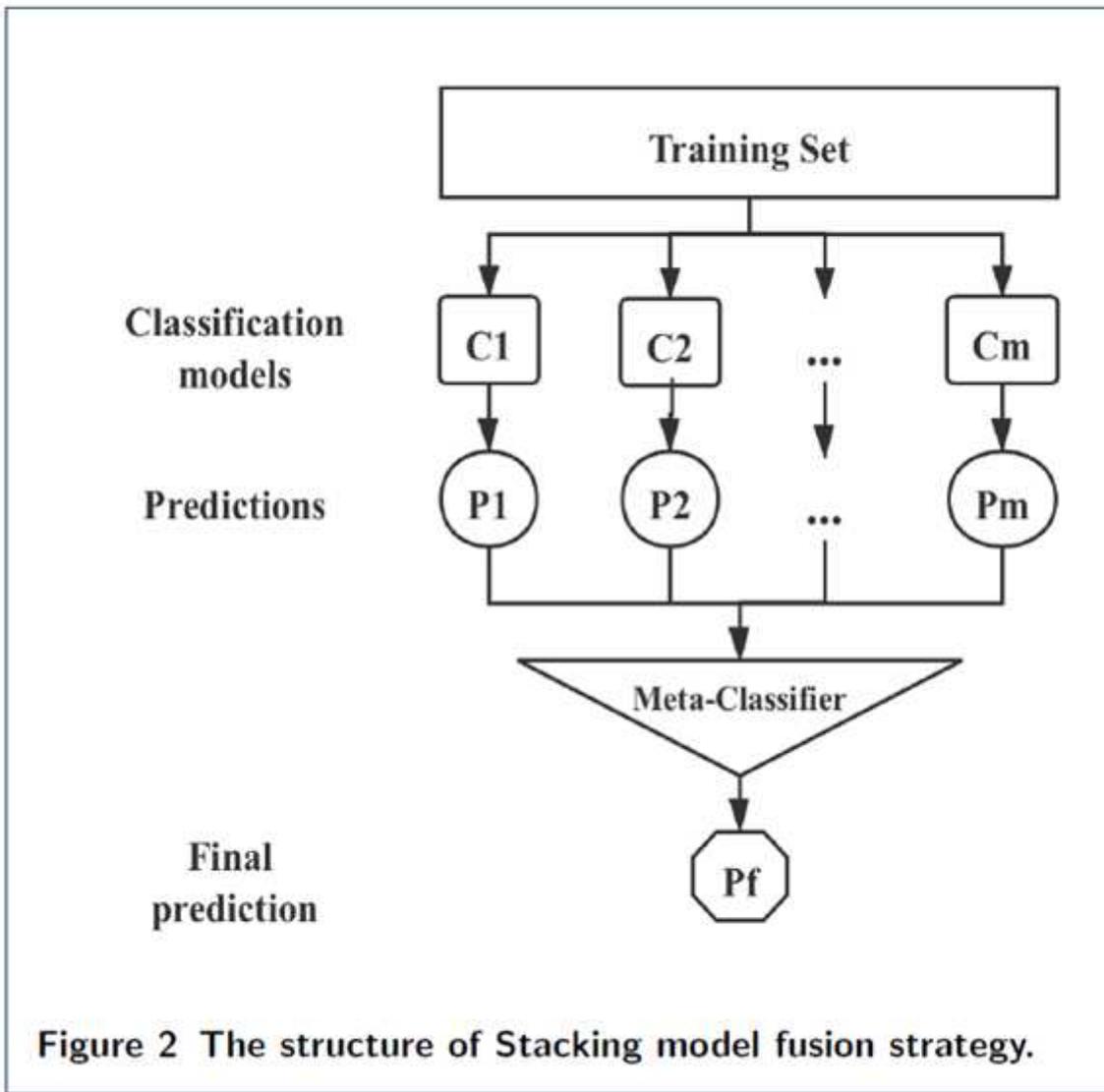
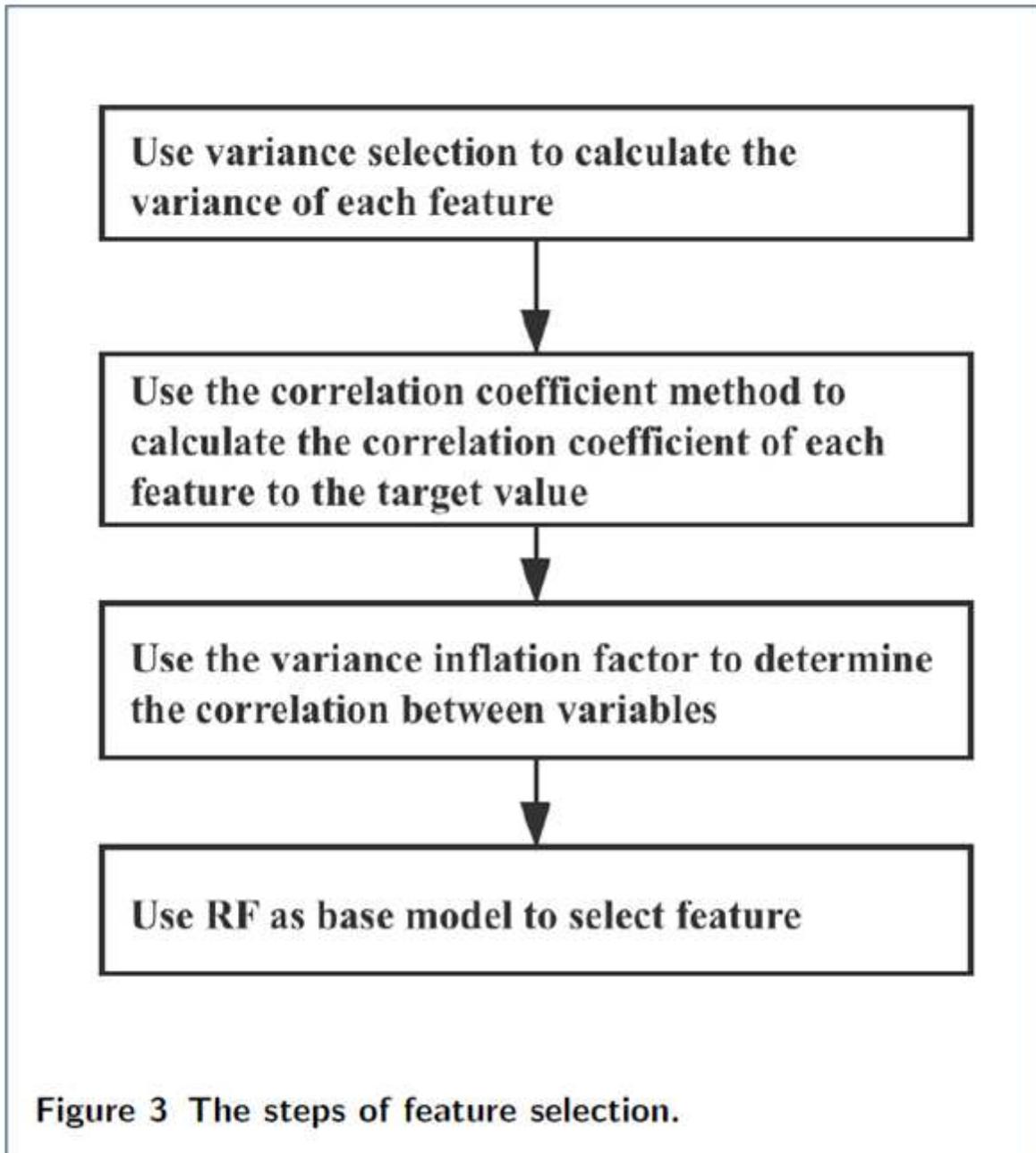


Figure 2

The structure of Stacking model fusion strategy.



**Figure 3**

The steps of feature selection.

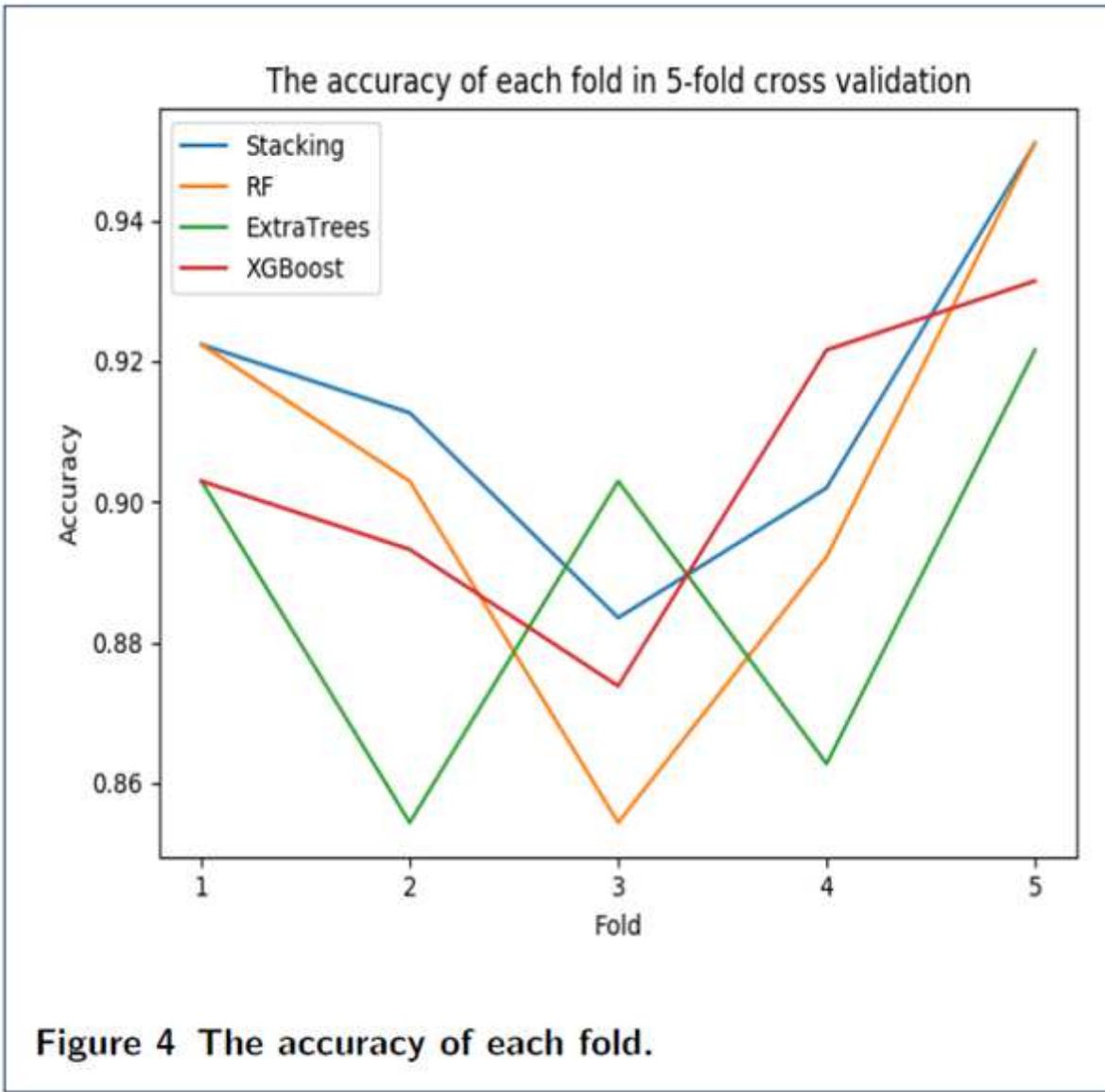


Figure 4

The accuracy of each fold.

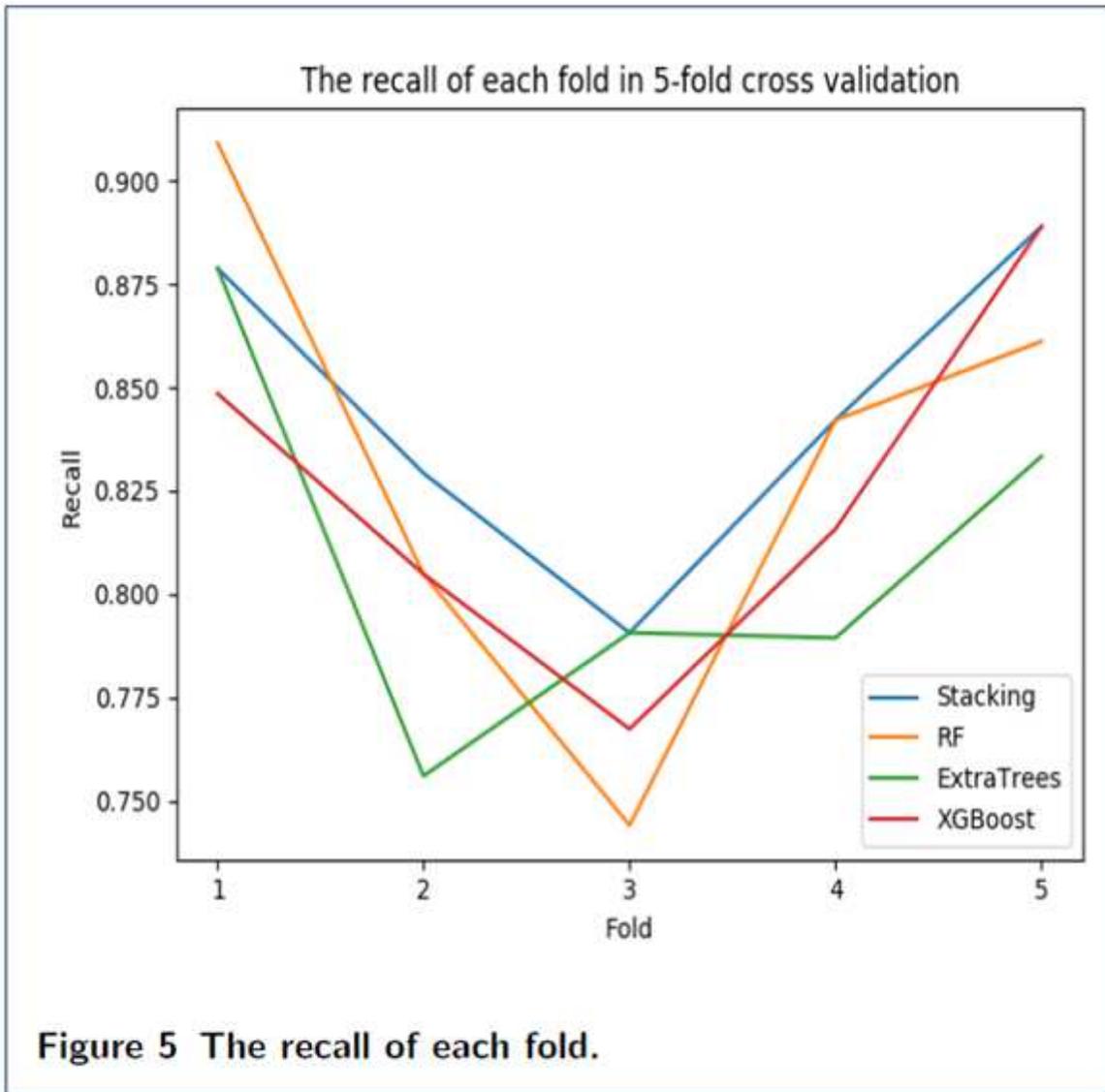


Figure 5

The recall of each fold.

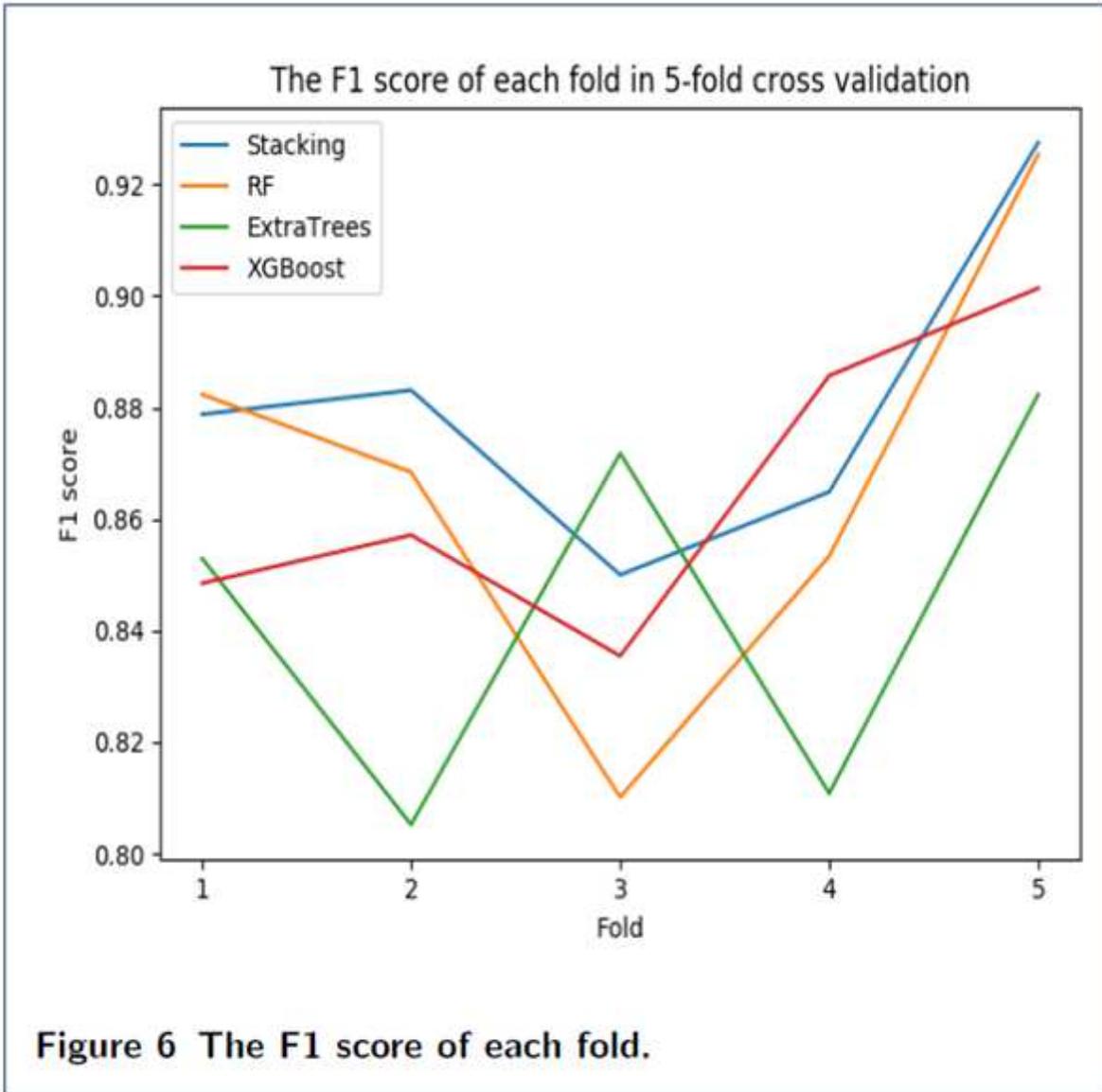


Figure 6 The F1 score of each fold.

Figure 6

The F1 score of each fold.