Predictors of atrial fibrillation in patients with type 2 diabetes mellitus: a propensity score-matched case-control study.

Zexiong Li
Third Affiliated Hospital of Sun Yat-Sen University https://orcid.org/0000-0002-5515-3368
Yanting Luo
Third Affiliated Hospital of Sun Yat-Sen University
Zhuoshan Huang
Third Affiliated Hospital of Sun Yat-Sen University
Xiaosi Yuan
Jieyang People's Hosptial
Long Peng
Third Affiliated Hospital of Sun Yat-Sen University
Xujing Xie
Third Affiliated Hospital of Sun Yat-Sen University
Jieming Zhu
Third Affiliated Hospital of Sun Yat-Sen University
Jinlai Liu (liujinl@hotmail.com)

Original investigation

Keywords: Type 2 diabetes mellitus, Atrial fibrillation, Monocyte to high-density lipoprotein ratio, Total cholesterol, Fasting glucose, Left atrial diameter

Posted Date: February 27th, 2020

DOI: https://doi.org/10.21203/rs.2.24738/v1

Abstract

Background Compared to people without diabetes, people with type 2 diabetes mellitus (T2DM) have an increased risk of developing atrial fibrillation (AF). Possible predictors of AF have not been adequately investigated in T2DM. We aimed to identify the factors associated with AF in such patients.

Methods A total of 2,682 patients with T2DM, who was admitted to Department of Cardiovascular Medicine, the Third Affiliated Hospital, Sun Yat-sen University between 1 June, 2015 to 1 Nov, 2019, were enrolled in the study. 641 patients were excluded. There were 122 patients with AF and 1,919 patients without AF. 1:1 propensity scores match was performed according to age and gender. Patients were divided into the two groups: with AF (122patients) and without AF (122patients). Clinical, demographic, echocardiographic, laboratorial data and medicine were compared between the groups.

Results There was significant statistical difference in neutrophil, monocyte, creatinine, total cholesterol (TC), triglyceride, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B100 (ApoB100), monocyte to high-density lipoprotein ratio (MHR), fasting glucose (FG), left atrial diameter (LAD), ejection fraction(EF), antiplatelet therapy and the prevalence of heart failure between the two groups. On multivariate logistic regression analysis, the increase of MHR, FG and LAD, as well as the decrease of TC and antiplatelet therapy were independent predictors of AF. On receiver operating characteristic (ROC) curve analysis, using a cut-off level of 0.568, MHR predicted AF with a sensitivity of 65.6%, a specificity of 76.2%, and an AUC of 0.736(95% CI 0.673-0.800). Using a cut-off level of 0.507, the combination of TC, MHR, FG, LAD and antiplatele therapy predicted AF with a sensitivity of 73.0%, a specificity of 84.4%, and an AUC of 0.862(95% CI 0.816-0.907).

Conclusions The increase of MHR, FG and LAD, as well as the decrease of TC and antiplatelet therapy were independent predictors of AF. MHR only, as well as the combination of TC, MHR, FG, LAD and antiplatelet therapy can better predict the risk of AF in patients with T2DM.

Background

Atrial fibrillation (AF) is a kind of atrial rhythm characterized by disordered agitation and disordered contraction, which is one of the common arrhythmias in clinical practice. The incidence of AF is 0.4%-1.0%, 2%-5% in the population over the age of 65, and 8.8% in the population over the age of 80. In recent years, the incidence of AF is increasing[1]. In cardiovascular diseases, AF will cause complications, such as stroke, thromboembolism, heart failure, myocardial infarction, renal impairment, seriously endangering human health and survival, with a high disability rate and mortality[1, 2]. AF is a common complication in patients with type 2 diabetes mellitus (T2DM) and will increase in the future[3]. Monocyte to high-density lipoprotein ratio (MHR) is a new inflammatory marker that combines inflammatory and anti-inflammatory effects. Lots of studies have shown that MHR is related to the occurrence, development and poor prognosis of cardiovascular diseases, but there are few studies on whether it is

related to the occurrence of atrial fibrillation. Thus, we aimed to investigate the predictors that may associated with AF in patients with T2DM, such as MHR, and evaluate their value at predicting AF.

Methods

Study population

Study data were gathered from the Hospital Information System(HIS).A total of 2,682 patients with T2DM, who was admitted to Department of Cardiovascular Medicine, the Third Affiliated Hospital, Sun Yat-sen University between 1 June, 2015 to 1 Nov, 2019, were enrolled in the study. 641 patients were excluded. There were 122 patients with AF and 1,919 patients without AF. 1:1 propensity scores match was performed according to age and gender (Fig. 1). Patients were divided into the two groups: with AF (122 patients) and without AF (122 patients). Clinical, demographic, echocardiographic, laboratorial data and medicine were collected. T2DM and AF diagnoses were ascertained by hospital discharge codes. The International Classification of Diseases, tenth Revision, Clinical Modification (ICD-10) code of E11, listed as a discharge diagnostic code, identified T2DM cases. And I48 identified AF cases. Patients who had valvular atrial fibrillation, recent infection, malignancies, blood dyscrasias, autoimmune or inflammatory diseases, hepatic failure, current therapy with corticosteroids were excluded from the study. The present study was approved by the Institutional Review Board of our hospital, and the requirement for written informed consent was waived because the study was retrospective and privacy of each patient was kept secret.

Statistical analysis

Statistical analysis was performed using the SPSS version 22.0 software. Continuous variables are presented as mean values ± SD, whereas categorical ones are presented as frequencies and percentage. Continuous variables were tested for normal distribution by the Shapiro Wilk test. Normally distributed variables compared using t test. Abnormally distributed variables compared using Mann Whitney U test. Categorical data were compared in both groups using the Pearson's Chi-square test. Univariate and multiple logistic regression analysis, Forward LR method was used to define the independent predictors of AF. Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off levels of MHR, fasting glucose and left atrial diameter to predict the occurrence of AF in patients with T2DM. A P value of < 0.05 was considered statistically significant.

Results

The study population consisted of 244 patients, 122 with AF and 122 without AF. Clinical, demographic, echocardiographic, laboratorial data and medication of the study population are shown in Table 1. Patients with AF exhibited a higher rate of heart failure ($P = 0.01$), increased neutrophil ($P = 0.037$), increased monocyte ($P < 0.001$), increased serum creatinine ($P = 0.014$), increased MHR ($P < 0.001$), increased fasting glucose (FG) ($P = 0.036$), increased left atrial diameter (LAD) ($P < 0.001$), decreased

total cholesterol (TC) (P = 0.001), decreased triglyceride (P = 0.021), decreased HDL-C (P = 0.001), decreased LDL-C (P = 0.002), decreased ApoA1 (P < 0.001), decreased ApoB100 (P = 0.033), decreased EF (P = 0.003), decreased antiplatelet therapy (P < 0.001) compared with those who remained in sinus rhythm (Table 1).

Table 1
Baseline features of the study population

Variables (% or mean ± SD)	AF(+)（n = 122）	AF(-)（n = 122）	Pvalue
Man, n (%)	75(61.48%)	65(53.28%)	0.195
Age, years	69.35 ± 10.80	67.03 ± 11.27	0.102
BMI, kg/m^2	24.73 ± 3.52	24.65 ± 3.34	0.672
Systolic blood pressure, mmHg	132.78 ± 19.27	133.27 ± 17.88	0.836
Diastolic blood pressure, mmHg	79.82 ± 12.70	77.46 ± 11.77	0.124
Heart rate, bpm	79.12 ± 13.27	76.88 ± 8.99	0.152
Current smoker, n (%)	34(27.87%)	36(29.51%)	0.777
Alcohol intake, n (%)	17(13.93%)	13(10.66%)	0.436
Hypertension, n (%)	95(77.87%)	92(75.41%)	0.650
Coronary Artery Disease, n (%)	60(49.18%)	69(56.56%)	0.248
Hyperlipemia, n (%)	18(14.75%)	25(20.49%)	0.240
Heart failure, n (%)	18(14.75%)	6(4.92%)	0.010
Chronic kidney diseases, n (%)	21(17.21%)	11(9.02%)	0.058
WBC, *10^9/L	7.37 ± 2.48	6.81 ± 2.07	0.080
Hemoglobin, g/L	128.07(29.15)	127.29(19.72)	0.840
Platelet, *10^9/L	222.08 ± 83.31	221.00 ± 64.74	0.650
Neutrophil, *10^9/L	4.94 ± 2.77	4.34 ± 2.09	0.037
Lymphocyte, *10^9/L	1.77 ± 0.69	1.79 ± 0.69	0.839
Monocyte,*10^9/L,	0.62 ± 0.22	0.48 ± 0.12	0.000
Serum creatinine, umol/L	104.63(68.17)	92.35(59.27)	0.014
Uric acid, umol/L	435.12(130.51)	419.84(124.21)	0.192
Total cholesterol, mmol/L	3.82(1.06)	4.33(1.18)	0.001
Triglyceride, mmol/L	1.47(1.16)	1.66(0.93)	0.021
For categorical variables n (%) is presented. For continuous variables Mean ± SD is presented			
BMI, body mass index; WBC, white blood cell; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB100, apolipoprotein B100; MHR, monocyte to high-density lipoprotein ratio; EF, ejection fraction; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.			

Variables (% or mean ± SD)	AF(+)（n = 122）	AF(-)（n = 122）	Pvalue
HDL-C, mmol/L	0.92(0.22)	1.03(0.23)	0.001
LDL-C, mmol/L	2.34 ± 0.89	2.71 ± 1.00	0.002
ApoA1, mmol/L	1.14 ± 0.23	1.27 ± 0.21	0.000
ApoB100, mmol/L	0.86 ± 0.29	0.92 ± 0.28	0.033
Lipoprotein (a), mg/L	214.76 ± 259.43	246.69 ± 260.92	0.065
MHR	0.71 ± 0.30	0.48 ± 0.15	0.000
Fasting glucose, mmol/L	7.78 ± 2.96	6.90 ± 2.05	0.036
HbA1c, %	7.24 ± 1.39	7.46 ± 1.64	0.269
Left atrial diameter, mm	38.78 ± 5.95	33.28 ± 4.31	0.000
EF, %	61.88 ± 10.67	65.51 ± 8.54	0.003
CCB, n (%)	60(49.18%)	71(58.20%)	0.158
ACEI, n (%)	12(9.84%)	7(5.74%)	0.232
ARB, n (%)	54(44.26%)	52(42.62%)	0.796
β-block, n (%)	86(70.50%)	77(63.11%)	0.221
Statins, n (%)	100(81.97%)	108(88.52%)	0.149
Antiplatelet, n (%)	63(51.64%)	99(81.15%)	0.000
Trimetazidine, n (%)	39(31.97%)	26(21.31%)	0.060
Coenzyme Q10, n (%)	26(21.31%)	15(12.30%)	0.060
Metformin, n (%)	58(47.54%)	66(54.10%)	0.306
Other oral hypoglycemic agents, n (%)	82(67.21%)	73(59.84%)	0.231
Insulin, n (%)	31(25.41%)	32(26.23%)	0.884
For categorical variables n (%) is presented. For continuous variables Mean ± SD is presented			
BMI, body mass index; WBC, white blood cell; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB100, apolipoprotein B100; MHR, monocyte to high-density lipoprotein ratio; EF, ejection fraction; CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.			

According to univariate logistic regression analysis, heart failure (OR = 3.346, P = 0.014), monocyte (OR = 110.507, P < 0.001), TC (OR = 0.663, P = 0.001), HDL-C (OR = 0.126, P = 0.001), LDL-C (OR = 0.663, P = 0.004), ApoA1 (OR = 0.064, P < 0.001), MHR (OR = 98.190, P < 0.001), FG (OR = 1.151, P = 0.010), LAD (OR = 1.224, P < 0.001), EF (OR = 0.960, P = 0.005), antiplatelet therapy (OR = 0.248, P < 0.001) were

significantly associated with the occurrence of AF. On multivariate logistic regression analysis, the increase of MHR (OR = 46.486, P < 0.001), FG (OR = 1.206, P = 0.015) and LAD (OR = 1.193, P < 0.001), as well as the decrease of TC (OR = 0.706, P = 0.029) and antiplatelet therapy (OR = 0.229, P < 0.001) were independent predictors of AF (Table 2).

Table 2
Univariate and multivariate logistic regression analysis results of the AF in patients with T2DM

	Univariate logistic regression				Multivariate logistic regression			
	Pvalue	OR	95% CI		Pvalue	OR	95% CI	
			Lower	Upper			Lower	Upper
Heart failure	0.014	3.346	1.280	8.749				
Monocyte	0.000	110.507	18.907	645.891				
Total cholesterol	0.001	0.663	0.523	0.841	0.029	0.706	0.515	0.966
HDL-C	0.001	0.126	0.038	0.410				
LDL-C	0.004	0.663	0.502	0.875				
ApoA1	0.000	0.064	0.018	0.222				
MHR	0.000	98.190	21.868	440.877	0.000	46.486	7.736	279.322
Fasting glucose	0.010	1.151	1.034	1.281	0.015	1.206	1.037	1.402
Left atrial diameter	0.000	1.224	1.153	1.300	0.000	1.193	1.115	1.276
EF	0.005	0.960	0.932	0.988				
Antiplatele	0.000	0.248	0.139	0.441	0.000	0.229	0.109	0.479

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; MHR, monocyte to high-density lipoprotein ratio; EF, ejection fraction.

Receiver operating characteristic (ROC) curve analysis was used to determine the optimum cut-off levels of MHR, FG and LAD to predict the occurrence of AF in patients with T2DM (Fig. 2, Fig. 3). Using a cut-off level of 0.568, MHR predicted AF with a sensitivity of 65.6%, a specificity of 76.2%, and an area under the curve (AUC) of 0.736 (95% CI 0.673-0.800). Using a cut-off level of 9.075, FG predicted AF with a sensitivity of 27.9% and a specificity of 87.4%, an AUC 0.577 (95% CI 0.506–0.649). Using a cut-off level of 36.5, LAD predicted AF with a sensitivity of 66.4%, a specificity of 77.0%, and an AUC of 0.769 (95% CI 0.710–0.828). Using a cut-off level of 0.507, the combination of TC, MHR, FG, LAD and antiplatelet therapy predicted AF with a sensitivity of 73.0% and a specificity of 84.4, AUC 0.862 (95% CI 0.816–0.907) (Table 3).

Table 3
ROC curve analysis results

	Sensibility(%)	Specificity(%)	cut-off	AUC	95% CI	
					Lower	Upper
MHR	65.6	76.2	0.568	0.736	0.673	0.800
FG	27.9	87.7	9.075	0.577	0.506	0.649
LAD	66.4	77.0	36.500	0.769	0.710	0.828
Combination of TC, MHR, FG, LAD and antiplatele therapy	73.0	84.4	0.507	0.862	0.816	0.907

TC, Total cholesterol; MHR, Monocyte to high-density lipoprotein ratio; FG, Fasting glucose; LAD, Left atrial diameter.

Discussion

T2DM is one of the most common chronic diseases with increasing prevalence. Patients with T2DM have a considerably higher risk of cardiovascular morbidity and mortality[4]. T2DM is also a risk factor for AF. Individuals with diabetes mellitus have a 40% higher risk of developing AF than that without diabetes[5]. Atrial electrical remodeling, structural remodeling and autonomic remodeling caused by T2DM may be the pathogenesis of AF[3, 6]. Yang S et al[7] divided 6,199,629 patients without AF into the normal fasting glucose (NFG) group, the impaired fasting glucose (IFG) group, the diabetes duration < 5 years (early T2DM) group, and the diabetes duration ≥ 5 years (late T2DM) group, followed up for 7.2 years on average, and compared the incidence of AF among the groups. The results showed that the incidence of AF increased significantly with the progression of T2DM.At the same time, with the increase of FG, the risk of AF increased significantly. This study shows that FG is a predictor of AF in patients with T2DM with a poor predictive value. It can still be used as an indicator to prevent AF in patients with T2DM. Chang SH et al[8] divided 645,710 patients with T2DM into the two groups based on the use of metformin or not, and followed up for 13 years. Multivariate Cox regression analysis showed that metformin reduced the incidence of new-onset AF significantly (HR = 0.81, P < 0.001). Chang CY et al[9] divided 90,880 patients with T2DM who were taking metformin into the two groups according to whether they were taking dipeptidyl peptidase-4 inhibitor (DPP4i) or not, and followed up for 3 years. They found that DPP4i users were associated with a lower risk of new-onset AF compared with non-DPP4i users (HR 0.65, P < 0.0001). Therefore, the use of metformin or DPP4ito reduce fasting glucose in patients with T2DM may reduce the incidence of new-onset AF. For patients with poor glycemic control, metformin combined with DPP4i may bring more benefit.

Inflammation is involved in the initiation of AF, and AF leads to inflammation in turn, which maintains the occurrence of AF. Inflammation leads to inflammatory infiltration, necrosis and fibrosis of cardiomyocytes[10], which is the basis of atrial electrical remodeling and structural remodeling, and can

lead to the occurrence and maintenance of AF. Monocytes are a type of inflammatory cells, which will accumulate rapidly during inflammation and secrete monocyte chemoattractant protein-1 (MCP-1) together with vascular endothelial cells, smooth muscle cells, macrophages, and cardiomyocytes. MCP-1 induces monocytes and vascular endothelial cells to express adhesion molecules and promotes the release of inflammatory factors such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α). IL-6 can directly affect connexins resulting in gap-junction dysfunction[11]. TNF-α can down-regulation of channel protein expression. Both caused atrial electrical remodeling[12]. MCP-1 and intercellular adhesion molecule-1 (ICAM-1) recruit macrophages. Macrophages secrete transforming growth factor-β (TGF-β) and profibrotic cytokines, which promote the formation of myofibroblasts and lead to myocardial fibrosis[13, 14].In addition, MCP-1 binding to chemokine receptor 2 (CCR2) induced a novel transcription factor (MCP-induced protein), which caused apoptosis of cardiomyocytes and lead to structural remodeling[15]. HDL-C can inhibit the migration and activation of monocytes, thus reducing the inflammatory[16].

MHR is an inflammatory marker that combines inflammation and anti- inflammatory effects, which is associated with a variety of cardiovascular diseases. Some studies have shown that MHR is a risk factor for new-onset AF and postoperative AF recurrence. Ulus T et al[17] divided 308 elderly patients with acute coronary syndrome undergoing percutaneous coronary intervention into the group with postoperative AF (n = 54) and the group without postoperative AF (n = 254). The difference in MHR between the two groups was statistically significant ($P < 0.01$), and multivariate logistic regression analysis showed that MHR was an independent predictor of new-onset AF (OR = 1.102, $P < 0.001$). Canpolat U et al[18] included 402 patients with AF in their study and performed cryoballoon-based catheter ablation. The patients were divided into the four groups according to their preoperative MHR quartiles. The lowest to highest quartiles of AF recurrence were 7.1%, 6.9%, 15.8% and 65% ($P < 0.01$). Multivariate Cox regression analysis showed that MHR was an independent predictor of postoperative AF recurrence (HR = 1.20, $P < 0.001$).In our study, the area under ROC curve of MHR was 0.736, the sensitivity 65.6%, and the specificity 76.2%.It showed that MHR is a predictor of AF in patients with T2DM with a great predictive value.

At present, the correlation between blood lipid and new-onset AF is still uncertain. The decrease of plasma membrane cholesterol determines the distribution of Kv1.5 subunits, and lead to a slow and progressive increase in ultra-rapid delayed rectifier K^+ current (IKur)[19].It causes the action potential duration to shorten and the conduction velocity to slow down, then causes the atrial fibrillation. This may explain the inverse association between TC and AF, as well as LDL-C and AF. Lopez FL et al[20]followed up 13,969 community participants over a period of 18.7 years, and found that high levels of LDL-C and TC were associated with lower incidence of AF. Mourtzinis G et al[21] followed 51,020 primary-care hypertensive patients without AF for 3.5 years, and AF occurred in 2,389 participants. Poisson regression analysis showed that 1.0 mmol/l increase in TC was associated with 19% lower risk of new-onset AF (95% CI 9%-28%), and 1.0 mmol/l increase in LDL-C was associated with 16% lower risk of new-onset AF (95% CI 3%-27%).Other studies[20, 22, 23] have shown the same conclusion, which including white, yellow and mixed American populations. In our study, the levels of TC and LDL-C in the AF(+) group were lower

than those in the AF(-) group, and multivariate logistic regression showed that TC was a predictor for AF, but not LDL-C.

Aspirin use is recommended for secondary prevention in T2DM patients with cardiovascular disease, which significantly reduced cardiovascular disease morbidity and mortality as well as all-cause death. For primary prevention, aspirin did not bring more benefits[24]. In this study, antiplatelet therapy can reduce the incidence of AF in patients with T2DM. This suggests that early antiplatelet therapy may prevent AF in high-risk patients with T2DM.

Finally, the combination of TC, MHR, FG, LAD and antiplatele therapy were used to performed ROC curve analysis. Its AUC was higher than that of single index. The risk of AF in patients with T2DM can be evaluated more accurately by using the combined index. It can guide our clinical practice.

There are some important limitations in our study that need to be addressed. First, this study is a retrospective study with a small sample size. However, we attempted to adjust for potential confounders by propensity score-matched method and multivariate adjustment. Second, the unknown number of undiagnosed AF is a well-known issue, and we may have underestimated the true incidence of AF in this study. Longer continuous ECG monitoring for AF screening would detect more undiagnosed cases of AF. Finally, we cannot rule out residual confounding. Therefore, a prospective study with a large sample size is still needed to find the risk factors for AF in patients with T2DM, so as to verify the consistency of the results.

Conclusion

The increase of MHR, FG and LAD, as well as the decrease of TC and antiplatelet therapy were independent predictors of AF. MHR only, as well as the combination of TC, MHR, FG, LAD and antiplatele therapy can better predict the risk of AF in patients with T2DM.

Abbreviations

T2DM: type 2 diabetes mellitus; AF: atrial fibrillation; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ApoA1: apolipoprotein A1; ApoB100: apolipoprotein B100; MHR: monocyte to highdensity lipoprotein ratio; FG: fasting glucose; LAD: left atrial diameter; EF: ejection fraction; MCP-1: monocyte chemoattractant protein-1; ICAM-1: intercellular adhesion molecule-1; IL-1: interleukin-1; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α; TGF-β: transforming growth factor-β; CCR2: chemokine receptor 2; ECG: electrocardiogram.

Declarations

Authors' contributions

ZXL analyzed and interpreted the patient data, and were the major contributors in writing the manuscript. YTL, ZSH and XSY collect the data and contributed to the introduction. LP, XJX and JMZ contributed to the reviewed/edited the manuscript. JLL made contributions to conception and design of this study and the edition of the manuscript. All authors read and approved the final manuscript.

Author details

[1]Department of Cardiology, The Third Afliated Hospital, Sun Yat-sen University, Guangzhou 510630, China.[2]Jieyang People's Hospital, Jieyang 522000, China.

Acknowledgments

None.

Competing interests

All authors have no conflict of interest to disclose.

Availability of data and materials

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

Consent for publication

All authors consented for the publication of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of our hospital, and the requirement for written informed consent was waived because the study was retrospective and privacy of each patient was kept secret.

Funding

None

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Figures

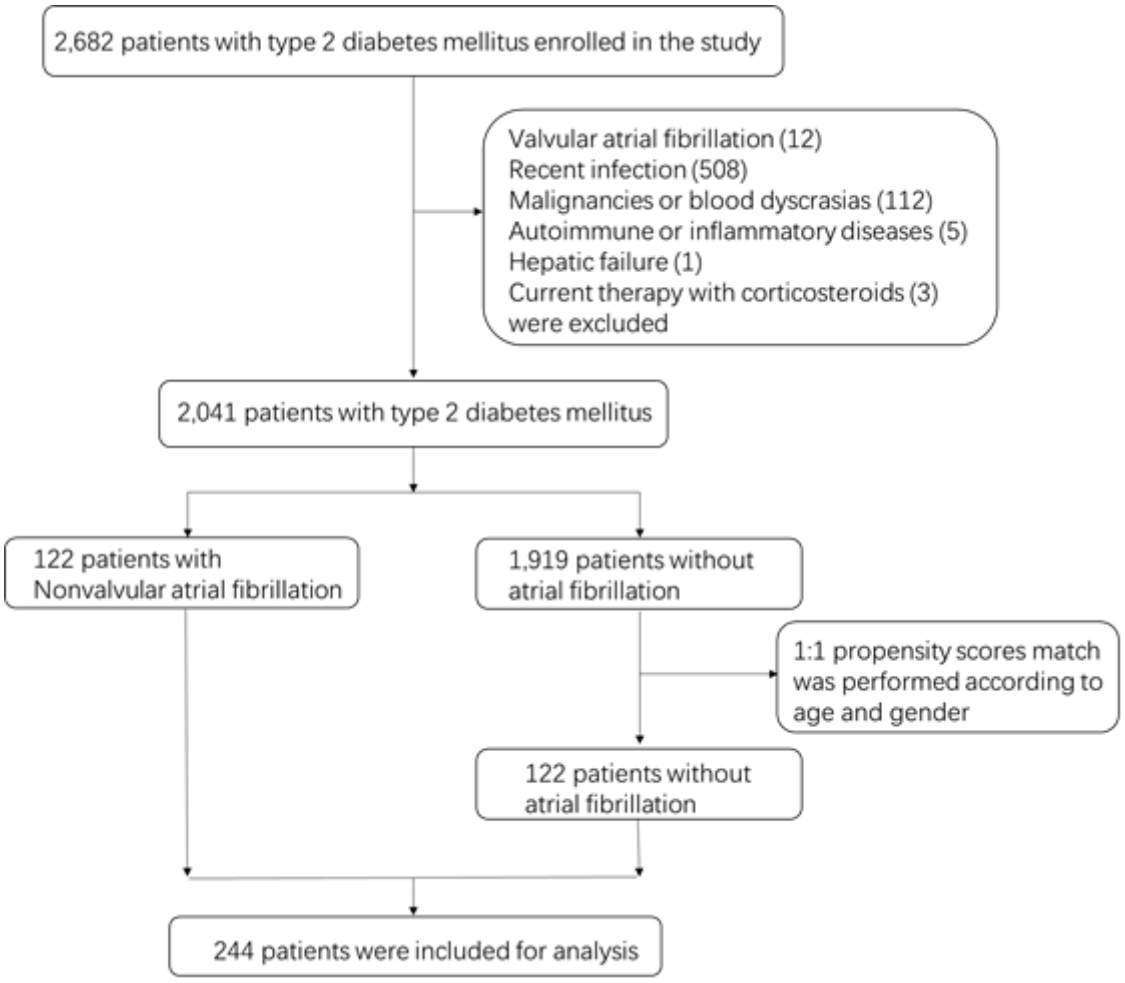

Figure 1

Flowchat of the present study.

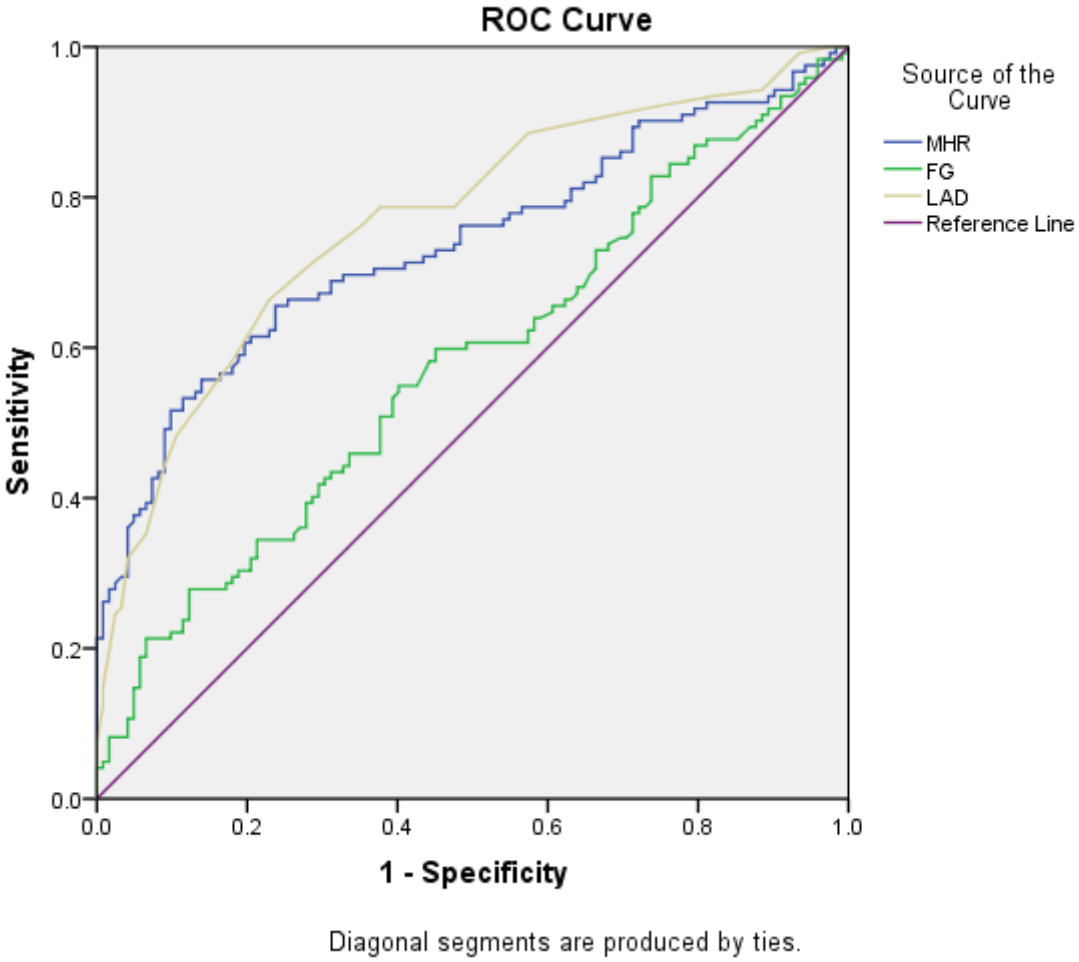

Figure 2

ROC curve of MHR, FG and LAD for predicting AF in patients with T2DM.MHR, Monocyte to high-density lipoprotein ratio; FG, Fasting glucose; LAD, Left atrial diameter.

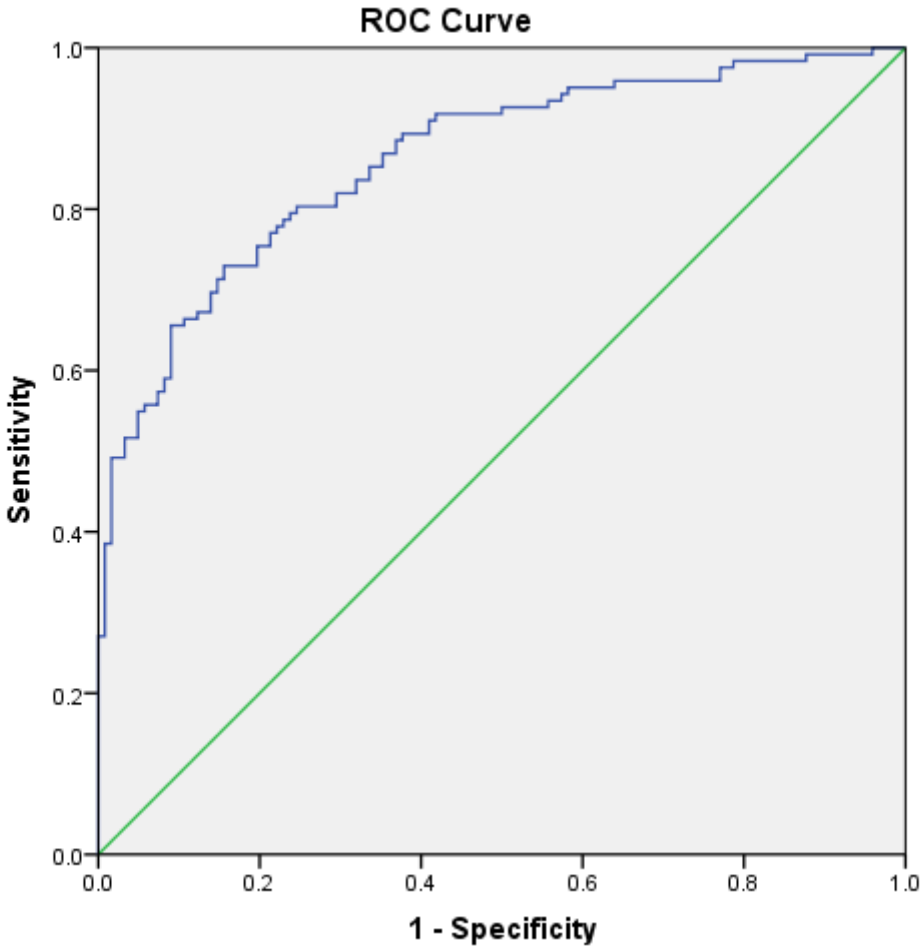

Figure 3

ROC curve of combination of TC, MHR, FG, LAD and antiplatele therapy for predicting AF in patients with T2DM. TC, Total cholesterol; MHR, Monocyte to high-density lipoprotein ratio; FG, Fasting glucose; LAD, Left atrial diameter.