Analysis of influencing factors for prognosis of patients with ventricular septal perforation: a single-center retrospective study

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Research Article

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Abstract

Background: Ventricular septal rupture (VSR) is a serious and fatal mechanical complication of acute myocardial infarction (AMI), once AMI patients are complicated with VSR, the mortality rate is as high as 90%. In this study, we explored the factors affecting the long-term prognosis of VSR patients from many aspects, and evaluated the evaluation performance of multiple scoring systems such as European Heart Surgery Risk Assessment System II (EuroSCORE II).

Methods: This study retrospectively enrolled 188 patients with VSR between Dec 9, 2011 and Nov 21, 2021at First Affiliated Hospital of Zhengzhou University. All patients were followed up until Jan 27, 2022 for clinical data, angiographic characteristics, echocardiogram outcomes, intraoperative, postoperative characteristics and major adverse cardiac events (MACEs) (30-day mortality, all-cause readmissions, recurrent MI, and unstable angina). Cox proportional hazard regression analysis was used to explore the predictors of long-term mortality.

Results: The median age of 188 VSR patients was 66.2±9.1 years and 97 (51.6%) were males. And there were 103 (54.8%) patients in the medication group, 34 (18.1%) patients in the percutaneous TCC group, and 51 (27.1%) patients in the surgical repair group. The average follow-up time was 857.4 days. The long-term mortality of the medically managed group, percutaneous TCC group, and surgical management group was 94.2, 32.4, and 35.3%, respectively. Whether combined with cardiogenic shock (OR 0.023, 95% CI 0.001–0.054, p=0.019), NT-pro BNP level (OR 0.027, 95% CI 0.002–0.34, p=0.005), EuroSCORE II (OR 0.530, 95% CI 0.305–0.918, p=0.024) and therapy group (OR 3.518, 95% CI 1.079–11.463, p=0.037) were independently associated with long-term mortality in patients with VSR. The cut-off point of EuroSCORE II was determined to be 14, and there were statistically significant differences between EuroSCORE II $<$ 14 group and EuroSCORE II $\geqslant$ 14 group (HR=0.2596, 95%CI: 0.1800-0.3744, Logrank P $<$ 0.001).

Conclusions: The prognosis of VSR patients without operative management remains poor, more research is needed to determine the optimal timing of surgery in patients with VSR to improve clinical outcomes. Moreover, EuroSCORE II could be used as a prognostic factor for VSR patients.

Keywords: acute myocardial infarction; ventricular septal rupture; percutaneous transcatheter closure; surgery; EuroSCORE II

1. Introduction

Ventricular septal rupture (VSR) is a type of heart rupture. Together with wall rupture and papillary muscle rupture, VSR is a serious and fatal mechanical complication of acute myocardial infarction (AMI), which often occurs within 1-2 weeks after AMI [1-3]. This is usually due to the influx of a large number of neutrophils into the necrotic area, which releases enzymes after apoptosis, accelerating the destruction of the infarcted myocardium and resulting in ventricular septal perforation [4]. Once AMI patients are complicated with VSR, the mortality rate is as high as 90% [5]. It is currently believed that female, old age, combined hypertension, first MI, anterior MI, etc. are the risk factors for AMI complicated by VSR [6-9]. For VSR, conservative medical treatment, percutaneous transcatheter closure (TCC) or surgical repair are usually adopted clinically. The mortality rates of patients with medical treatment alone were extremely high [10]. Hence, a surgical closure is recommended to be the standard therapy by the current ST-elevation MI (STEMI) guidelines of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and the European Society of Cardiology (ESC) [11,12]. But at present, there is no clear standard for the selection of operation timing. Studies have shown that the difficulty of the procedure, as well as the postoperative mortality and morbidity, all decline significantly in elective surgery compared to immediate surgery [13]. Therefore, a period of recovery and healing prior to surgical repair is often advocated [14]. Nevertheless, the outcome of elective surgery may be a manifestation of survival bias, as it is usually performed in relatively stable patients with VSR [15]. In addition, the interventricular communication may expand in a considerable

number of patients while waiting for intervention, thereby increasing shunt fraction and worsening right ventricular overload [16]. Based on this, the 2013 AHA guidelines for STEMI recommended emergency surgical repair for all patients with VSR, even in hemodynamically stable patients [11].

Recent advances in transcatheter technology mean it is increasingly viable as an alternative to surgical closure of VSR but is mainly restricted to selected cases in which patients have small VSR in the subacute or chronic phase [17,18]. In addition, there are many improved new surgical methods, but the effect is not very clear, and the repeatability is low [19,20]. European Heart Surgery Risk Assessment System II (EuroSCORE II) is a widely used scoring system, which can accurately evaluate the preoperative risk and predict the mortality after cardiac surgery. It is critical for measuring the magnitude of risks after surgery, choosing treatment projects, providing consultation for patients and improving the quality programs [21,22].

In our single-center retrospective study, we wanted to evaluate the prognostic factors of VSR patients from multiple perspectives, and compare the effects of conservative medical treatment, percutaneous TCC and surgical repair on the long-term prognosis of patients. We will calculate the EuroSCORE II score of all patients and analyze the relationship between the score and long-term prognosis of VSR patients, aiming to provide useful information for the management and treatment of clinical VSR patients.

2. Methods

2.1. Study Design and Population

This was an analysis of retrospectively collected data including

all adult (> 18 years of age) patients with a postinfarction VSR admitted to First Affiliated Hospital of Zhengzhou University between Dec 9, 2011 and Nov 21, 2021. Eligible patients were mainly those with evidence of VSR after MI：（a）the appearance of rough blowing systolic murmurs between the third and fourth left ribs during post-MI physical examinations; （b）a disruption in the ventricular septum with evidence of left-to-right shunt and was confirmed by transthoracic echocardiogram (TTE) and (c) left ventriculography showed contrast shunting from left to right [23]. Exclusion criteria: VSR secondary to the presence of congenital heart disease; rheumatic heart disease; combined with cardiomyopathy, such as hypertrophic cardiomyopathy, etc.; known tumor or systemic disease (such as lupus erythematosus, nephrotic syndrome, etc.); serious infection; acute trauma. Our study was approved by the ethical committee of the First Affiliated Hospital of Zhengzhou University (Approved No. of ethic committee 2022-KY-0041) and all procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). In addition, written informed consent was obtained from each participant before we conducted the study.

2.2. Data Collection

From Dec 9, 2011 to Nov 21, 2021, a total of 191 patients with VSR were admitted to the First Affiliated Hospital of Zhengzhou University. All these patients were screened according to our inclusion criteria and exclusion criteria. Finally, we excluded three patients, including one less than 18 years old, one with congenital heart disease, and one with myocardial infarction complicated with ventricular septal perforation caused by stress myocarditis. Ultimately, 188 patients with VSR were enrolled in our study.

We obtained the clinical data of patients during their stay by querying the medical record system of our hospital, and received the

long-term outcomes through telephone follow-up with the 188 VSR patients individually by trained professionals.

We retrieved all the demographic and clinical data of all subjects in this study, including age, sex, comorbidities, whether to transfer from other hospitals, MI staging, MI to VSR time, Killip classification, laboratory values upon ED admission (within 24 hours), therapeutic interventions, Gensini score, Sequential Organ Failure Assessment (SOFA) score and EuroSCORE II score.

We divided 188 VSR patients into medication group, percutaneous TCC group and surgical repair group according to treatment modalities. The three groups were then further divided into survival group and death group according to survival at the end of follow-up.

Angiographic characteristics of VSR patients was also recorded in our statistics, which included the following information: the count and the type of lesion blood vessels, left main occlusion or not, with or without 100% vascular occlusion [100% occlusion refers to complete occlusion of one or more vessels in the left anterior descending (LAD), left circumflex (LCX), and right coronary arteries (RCA)]. We eventually collected angiography characteristics from 91 VSR patients because some patients were too critical for a coronary angiography, or patients underwent angiography outside our hospital but we could not obtain the results.

We also collected information about echocardiogram outcomes of VSR patients. All 188 patients underwent at least one TTE after admission, and we recorded the results within 24 hours after perforation in each patient. These include MI territory (only patients with a single-site MI were counted), multiple MI or not, extensive anterior MI or not, left ventricle ejection fraction (LVEF), left ventricular end-diastolic dimension (LVEDD), maximum rupture size (defined as the maximum value of the defect diameter in mm, measured by transthoracic ultrasound), multiple VSR or not, whether

combined with ventricular aneurysm, the number of patients with pulmonary artery pressure (PAP) over 60, VSR location (divided as apical, anterior, posterior or anterior+ posterior) and whether the site of VSR is the posterior segment.

To further explore the relationship between intraoperative characteristics and the long-term mortality of patients in surgical repair group, we recorded operation-related information from the medical record system, which mainly includes surgical status (hemodynamically unstable VSR as a complication of AMI is considered an emergency operation, otherwise elective operation), operation consuming time, surgical incision (including ventricular aneurysm incision, left ventricular incision, right atrium tricuspid valve incision and aortic root incision),

surgical repair method [defined as direct suture, patch and surgical repair combining an occluder and a patch (SurCOP)], whether a coronary artery bypass graft (CABG) was also performed and the number and type of graft vessels, and whether the patient had a ventricular aneurysm resection and valvuloplasty [24].

After the percutaneous TCC or surgical repair, ventilator usage time, operation outcomes, length of stay in the hospital and the intensive care unit (ICU), post-operative residual shunt (The TTE results within 24 hours after operation were taken as the standard), additional complications [e.g., renal failure requiring continuous renal replacement therapy (CRRT), hemolysis requiring blood transfusion and low cardiac output syndrome (LCOS)] were recorded.

2.3. Study Outcomes and Definitions

The primary outcome was the long-term mortality. The long-term mortality was defined as overall mortality during the follow-up period. Secondary outcomes are major adverse cardiac events (MACEs). We defined MACEs as 30-day mortality, all-cause readmissions, recurrent MI, and unstable angina.

In our study, the definition of each variable was in line with the cardiovascular data standards [25]. Cardiogenic shock was defined as persistent hypotension (systolic blood pressure <90 mm Hg) with reduction in cardiac index (<1.8 L/min/m2) despite maximal treatment [26]. There are three main methods for VSR surgical repair in our hospital: direct suture, patch and SurCOP. The first two surgical methods are the conventional methods we used more before. When the perforation is relatively small, use sutures of different specifications to continuously suture the perforation site. When the perforation is relatively large, it is often repaired by continuous suture or intermittent mattress suture with bovine pericardial patch because the fibrous tissue around the perforation is firm. While the third method called SurCOP is a new surgical technique, combines the use of a patent ductus arteriosus (PDA) occluder with a slightly larger bovine pericardial patch to close the rupture [27]. In addition, there are four main types of surgical incisions to expose the perforation, which are: ventricular aneurysm incision, left ventricular incision, right atrium incision and aortic root incision. The left ventricle was incised parallel to and 1–2 cm away from the anterior or posterior descending artery. In some cases, the right atrium was cut to expose the tricuspid valve, and then the perforation site was exposed. When combined with ventricular aneurysm, incision of ventricular aneurysm is usually selected to expose perforation. While aortic root incisions are less common.

2.4. Statistical Analyses

Data were analyzed using IBM SPSS Statistics 25.0 (Armonk, NY: IBM Corp.) and GraphPad Prism v9.0 (GraphPad Software, La Jolla, CA, USA), using mean ± standard deviation (SD) to express if normal distribution continuous variables, median (25th–75th percentiles) if skew distribution continuous variables, and count (percentage) if categorical variables. The Shapiro-wilk test was used, and histograms

and normal-quantile plots were examined to verify the normality of distribution of continuous variables. Differences between groups were assessed using the Chi-square test or Fisher's exact test (when at least an expected value in a cell is<5) for categorical variables and two independent sample t-test, or one-way analysis of variance (ANOV A) for continuous variables, as appropriate. We analyzed the influencing factors or predictors of prognosis of VSR patients by binary Logistic regression, the factors entered into the regression analysis were as follows: sex, MI to VSR time, history of cerebral infarction, malignant arrhythmia, cardiogenic shock, lactic acid, white blood cells (WBC), hemoglobin, alanine transaminase (ALT), creatinine, glucose, n-terminal pro b-type natriuretic peptide (NT-pro BNP), cardiac troponin I (cTnI), LVEF, EuroSCORE II, SOFA score and therapy group. Levels of NT-pro BNP was normalized by $\log_{10}$ transformation. Using the receiver operating characteristic (ROC) curve and the area under the curve (AUC) to evaluate the discriminative ability of EuroSCORE II, SOFA score, etc. to predict the prognosis of VSR patients, and calculate the sensitivity, specificity and 95% confidence interval (CI) of AUC. For each variable, the optimal prediction threshold was calculated using the Youden's index. Kaplan–Meier survival curves and the Log-rank test were used to identify significant relationships between whether the EuroSCORE II was greater than the optimal prediction threshold and long-term mortality. The results are expressed as hazard ratio (HR) and 95% CI. Two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Results of Recruitment

From 9 December 2011 to 21 November 2021, 191 VSR patients admitted to our hospital were screened, 3 patients were excluded from the analysis according to the predetermined criteria. After

exclusion, a total of 188 VSR patients were enrolled in this study. Our follow-up date ended on 27 January 2022, the longest follow-up time was 3702.1 days, and the shortest was 0.1 days, the median follow-up time was 17.0 days. Considering the bias caused by the short survival time of the patients in the medication group, we analyzed the follow-up time of the percutaneous TCC group and the surgical repair group, and the results showed that the median follow-up time was 575.0 days (25th–75th percentile:25.0-1374.5 days) [The average follow-up time was 857.4 days]. All patients were divided into three groups according to the treatment modalities, among which, there were 103 (54.8%) patients in the medication group, 34 (18.1%) patients in the percutaneous TCC group, and 51 (27.1%) patients in the surgical repair group. The enrollment and clinical grouping for VSR patients are shown in the flow diagram in Fig. 1.

3.2. Clinical Characteristics

Characteristics of the study population are shown in Table 1; median age was 66.2±9.1 years and 97 (51.6%) were males. Through analysis, we found that compared with the survival group, the proportion of females in the death group was larger (69, 54.8%), and there were more patients with previous cerebral infarction (27, 21.4%), malignant arrhythmia (52, 41.3%), cardiogenic shock (46, 36.5%), preoperative cardiac arrest (12, 9.5%), renal failure (76, 60.3%) and multiple organ dysfunction syndrome (MODS) (23, 18.3%), shorter MI to VSR time (5.3±6.1), and higher Killip classification (4: 102, 81%) in the death group. In terms of laboratory values upon ED admission, hemoglobin [122.1 (109.0, 137.0)] and albumin [35.4 (33.0, 38.4)] in the death group were lower, while lactic acid levels [2.8 (1.7, 6.0)], WBC [13.7 (10.8, 16.7)], total bilirubin [20.7 (13.1, 30.0)], uric acid (499.0±280.4), creatinine (180.6±161.1), ALT (687.6±1240.5), aspartate transaminase (AST) [202.0 (54.0, 5054.0)], glucose (10.9±10.2), NT-pro BNP

(15057.1±11620.3), and cTnI (8.4±17.2) were higher. According to the therapy groups, the proportion of patients treated with medication was highest in the death group [medication group (97, 77.0%) vs. percutaneous TCC group (11, 8.7%) vs. surgical repair group (18, 14.3%), $P<0.001$]. And there was no significant survival difference between the percutaneous TCC and surgical repair group (p=0.779). SOFA score [death group (14.3±5.3) vs. survival group (10.0±3.0), P <0.001] and EuroSCORE II [death group (16.0±2.3) vs. survival group (12.5±2.0), $P<0.001$] in the death group were significantly higher than those in the survival group, and more patients in the death group required intra-aortic balloon pump (IABP) (43, 34.1%), CRRT (21, 16.7%) and central venous catheter (CVC) (70, 55.6%) treatment. In addition, the proportion of IABP difficult to offline in the death group was higher (39, 90.7%).

3.3. Angiographic and Echocardiograms Outcomes

Angiographic characteristics and echocardiogram outcomes of 188 VSR patients are shown in Table 2 and Table 3. There was no significant difference in angiographic characteristics between survival and death groups. In the light of the echocardiogram outcomes, patients in the death group had lower LVEF (48.2±10.0), and the proportion of posterior perforation was lower (15, 11.9%).

3.4. Intraoperative Characteristics of Surgical Repair Group

Intraoperative characteristics of VSR patients in surgical repair group are shown in Table 4. There was a total of 51 patients in the surgical repair group, emergency operation was performed in 3 patients, and elective operation was performed in the remaining 48 patients. All 3 patients who underwent emergency operation died within 30 days due to LCOS, hemorrhage event, and refractory heart failure, respectively (3, 16.7%, P=0.039). Of the 51 patients in the surgical repair group, 2 patients went to another hospital for surgical

repair after discharge, and 1 patient gave up sealing and failed surgical repair because of serious myocardial infarction on the right ventricular surface, which was at risk of heart rupture. Therefore, the surgical information of these 3 patients was insufficient, and the surgical information of the remaining 48 patients was collected. All the 48 patients underwent repair surgery under the condition of cardiopulmonary bypass support (CPB) and moderate hypothermia myocardial protection. After general anesthesia, the operation was performed through a median sternal incision. Among the 48 patients, 5 (10.4%) patients were sutured directly, and the perforation of these patients was relatively small, and 4-0 prplene suture was used for continuous suture. In 27 (56.3%) patients, the ventricular septum and free wall of heart were reconstructed with bovine pericardial patch, and then the interface was sutured continuously or intermittently with sutures of different thickness. The remaining 16 (33.3%) patients received a modified surgery method named SurCOP with a 100% success rate. This new technology was first carried out by our hospital, which improved the traditional method of using bovine pericardial patch alone, combined a T-shaped PDA occluder and a slightly larger patch in the VSR site. SurCOP precisely released the sealing material, remain stable under persistent exposure to high left-to-right pressure gradient, prevent the remaining shunt, and maintain cardiac function after surgery [27]. There were no significant differences in operation consuming time, surgical incision selection, surgical repair method, whether CABG performed at the same time etc. between the survival and death groups.

3.5. Postoperative Characteristics

Comparison of postoperative characteristics of VSR patients between surgical repair group and percutaneous TCC group are shown in Table 5. It should be noted that 3 patients in the percutaneous TCC group underwent surgical repair after operation,

including 1 case due to interventional closure failure, 1 case due to residual shunt after closure, and 1 case with severe tricuspid insufficiency after operation. We included these 3 patients in the surgical repair group. A total of 4 (11.8%) patients in the percutaneous TCC group failed in sealing, 2 because the guide wire could not pass through the ventricular septal defect to the right ventricle and pulmonary artery, 1 because the umbrella fixation failed after sealing, and 1 because the sealing device slipped into the right ventricle after repeated attempts. In the surgical repair group, 1 (2.0%) patient failed in sealing because of serious infarction and the risk of heart rupture. After analysis and comparison, we determined that the duration of ventilator use was longer in the surgical repair group [percutaneous TCC group 0.0 (0.0, 16.8) vs. surgical repair group 37.9 (20.1, 62.0), $P<0.001$]. In addition, patients in the surgical repair group also had longer hospital stays [percutaneous TCC group (22.0±9.8) vs. surgical repair group (31.1±17.0), $P=0.006$]. The postoperative complications were: renal failure requiring CRRT (15,18.5%), hemolysis requiring blood transfusion (38, 46.9%) and LCOS (29, 35.8%). Compared with the percutaneous TCC group, the surgical repair group had a lower incidence of postoperative residual shunt [percutaneous TCC group (19, 57.6%) vs. surgical repair group (12, 24.5%), $P=0.002$] but a higher incidence of postoperative hemolysis requiring transfusion [percutaneous TCC group (8, 24.2%) vs. surgical repair group (30, 62.5%), $P=0.001$]. There was no significant difference in long-term mortality between the percutaneous TCC group and the surgical repair group ($P=0.779$), but the percutaneous TCC group had a higher risk of readmission [percutaneous TCC group (15, 44.1%) vs. surgical repair group (8, 15.7%), $P=0.004$] and higher odds of developing MACEs [percutaneous TCC group (26, 76.5%) vs. surgical repair group (25, 49.0%), $P=0.011$].

3.6. The Long-term Mortality

Binary Logistic regression showed that cardiogenic shock (odds ratio [OR], 0.023; 95% CI, 0.001-0.544; *P*=0.019), high levels of NT-pro BNP (OR, 0.027; 95% CI, 0.002-0.340; *P*= 0.005), high EuroSCORE II score (OR, 0.530; 95% CI, 0.305-0.918; *P*=0.024) and conservative medical treatment (OR,3.518; 95% CI, 1.079-11.463; *P*=0.037) were independently associated with long-term mortality. ORs with 95% CIs are presented in Fig. 2.

The ROC curves for EuroSCORE II, NT-pro BNP, SOFA score, Killip classification and cardiogenic shock were plotted separately to evaluate their predictive power for long-term mortality, yielding an AUC of 0.867, 0.795, 0.760, 0.721 and 0.675, respectively. The specific results are shown in Fig. 3 and the legend. The results indicated that EuroSCORE II predicted long-term mortality with high accuracy. The cut-off point was determined to be 14 by calculating the maximum of the Youden's index. According to the cut-off point, the patients were divided into EuroSCORE II $<$ 14 group and EuroSCORE II$\geqslant$14 group. The median survival time estimates for EuroSCORE II$<$14 group and EuroSCORE II$\geqslant$14 group were 681.3 days and 8.0 days, respectively. The survival curves of were plotted using the Kaplan-Meier method and Log-rank test showed in Fig. 4 and there were statistically significant differences between EuroSCORE II$<$14 group and EuroSCORE II$\geqslant$14 group (HR=0.2596, 95%CI: 0.1800-0.3744, Logrank *P*$<$0.001).

4. Discussion

In this single center retrospective study of 188 patients, we explored the factors affecting the long-term prognosis of VSR patients from many aspects, and evaluated the evaluation performance of multiple scoring systems such as EuroSCORE II. Overall, long-term

mortality was higher in women, patients with previous myocardial infarction, malignant arrhythmias, cardiogenic shock, cardiac arrest, renal failure, and MODS ($P<0.05$). In addition, these patients had a shorter MI to VSR time and a higher Killip classification than the survival group ($P<0.05$). From the laboratory data, there were also significant differences in lactic acid, white blood cell, NT-pro BNP and other indicators between the death group and the survival group ($P<0.05$). According to the results of TTE, the LVEF in the death group was lower ($P<0.05$), and the perforation location was also related to the mortality. Compared with the apical and anterior VSR, the mortality of patients with posterior VSR was lower. In terms of MI territory, the prognosis of extensive anterior MI was worse, although there was no significant difference in this study($P=0.093$), an anterior MI is more common in patients who develop a VSR than those who do not and tends to produce simple apical defects. In contrast, inferior or lateral MIs often results in basal defects, which may be more irregular and extensive [5,28,29]. In addition, the timing of surgery will also affect the long-term mortality of VSR patients. In this study, 3 patients who underwent emergency operation died during the follow-up period. A number of studies have shown that female gender, old age, worse Killip grade and cardiogenic shock are the risk factors of 30-day mortality in patients with VSR [3,30,31], which is roughly consistent with our study, but there are many different results, which possibly due to variations in the study cohort, and our study pays more attention to the risk factors of long-term prognosis in patients with VSR.

We also compared the effects of medical treatment, percutaneous TCC and surgical repair on the long-term prognosis of patients. The results showed that the mortality of patients in the medical conservative treatment group was much higher than that in

the other two groups. However, there is also a survival bias caused by conservative treatment due to unstable hemodynamics in some patients. The prognosis of these patients with early hemodynamic instability is often worse [15]. At present, there is no uniform standard for the optimal period of surgical repair. The 2013 AHA guidelines for STEMI recommended emergency surgical repair for all patients with VSR, even in hemodynamically stable patients [11]. However,

due to an inadequate transportation system in middle-income economies like China, a large proportion of VSR patients cannot receive emergency surgery in a timely manner and therefore, unplanned delayed surgery is common in China [3]. Ronco D et al found that delayed surgery appeared to be associated with better survival, while emergent surgery was associated with a higher mortality [32]. According to the Society of Thoracic Surgeons (STS) database, patients

who underwent surgery within 7 days of presentation had a 54.1% mortality compared with 18.4% mortality if the repairs were delayed until after 7 days [33]. Therefore, the best surgical timing was as late as possible in theory. While things go different in fact, unlimited delayed surgery may expand the interventricular communication, thereby increasing the shunt fraction and worsening right ventricular overload, only small single-center series or national registries are usually available in literature, whereas international multicenter investigations have been poorly carried out, therefore limiting the evidence on this topic [16,32]. Malik J et al suggested that the use of mechanical circulatory support (MCS) in adjunct to a deferred surgical approach shows an improved survival outcome of patients with VSR complicated by cardiogenic shock [34]. At present, IABP, implantable turbine-pump, and percutaneous cardiopulmonary bypass support

are counted among the different cardiac assist devices available to cardiologists and cardiac surgeons to stabilize the patient after acute MI before operation [35]. Indeed, the role of MCS is gaining progressively more credits in the management of VSR, both for achieving patients' stabilization before surgery and for providing a protected early perioperative course [16,36,37]. In this study, the proportion of using IABP, CRRT and CVC in the death group is higher than that in the survival group, and most of the death group patients who rely on IABP support are difficult to go offline, which also shows that unlimited delayed surgery may cause unnecessary patients' pain and costs, especially for those relaying on mechanical assist. Therefore, the best timing of delayed surgery is that patients receive surgery intervention as soon as they reach healed phase. However, as the delayed surgery strategy is not accepted broadly, further investigations are required for verification [38]. Additional operations for surgical repair of VSR including CABG operation in 28 patients, ventricular aneurysm resection in 33 patients, bicuspid annuloplasty in 3 patients and tricuspid annuloplasty in 7 patients, which showed no difference between the death group and the survival group. There is no clear conclusion about the pros and cons of these additional procedures. In the case of CABG, Abu-Omar Y et al. reported that CABG has no long-term prognosis, and prolongs the operation time and increases the patient's surgical risk [39]. However, it was also suggested to perform CABG at the same time [40]. Studies have shown that the advantages of left ventricular aneurysm resection in reducing ventricular volume, restoring ventricular shape, and reducing the arrhythmic risk related to necrotic scar, have been well addressed in the past decades, but it is also possible that the patient cohort considered in the paper is somehow different from the patients generally presented and managed in other studies about VSR

[33,41,42].

Percutaneous TCC has emerged as an alternative to surgical closure of VSR but is mainly restricted to s

elected cases in which patients have small VSR in the subacute or chronic phase [43]. When applied in more advanced cases, it is associated with high operative mortality [2].

In this study, the postoperative characteristics of VSR patients in the surgical repair group and the percutaneous TCC group were compared from the aspects of hospital stay, post-operative residual shunt and so on. The ventilator usage time, hospital stay, and the probability of postoperative hemolysis in the surgical repair group were higher than those in the percutaneous TCC group, and the latter had a higher probability of post-operative residual shunt and readmission than the surgical repair group. The rate of MACEs was higher in the percutaneous TCC group. Currently, the comparison between surgical repair and percutaneous TCC for the treatment of VSR is limited, and more large-sample clinical studies are needed to further compare the advantages and disadvantages of the two methods.

EuroSCORE was originally a quantitative risk evaluation system to predict in-hospital mortality after cardiovascular operation [44]. After continual updating, the latest version is EuroSCORE II, which is widely used in preoperative risk assessment of cardiac operation [45]. It is a part of routine treatment in many heart centers [46,47]. In this study, three commonly used scoring systems, Gensini score, SOFA score and EuroSCORE II, were selected to analyze and compare their ability to predict the long-term prognosis of VSR patients. The results show that the prediction accuracy of EuroSCORE II for long-term mortality is much higher than the other two scores. This shows that EuroSCORE II can be used not only for preoperative risk assessment of cardiac surgery, but also as one of the risk assessment factors for the prognosis of VSR patients. If it is slightly changed on its basis, the prediction accuracy may be further improved, which also

needs a large number of relevant studies to implement.

The present study explored the factors affecting the long-term prognosis of VSR patients, and evaluated the performance of multiple scoring systems such as EuroSCORE II. There are several other limitations to this investigation. Firstly, during the follow-up, some cases were lost to follow-up, which would lead to bias. Secondly, the better outcome of VSR repair surgery may be a manifestation of survival bias, as it is usually performed in patients with relatively stable VSR who are expected to have a better prognosis than patients with early hemodynamic instability. Our research was no exception to this bias. Finally, in this single-center study, the research results can be hardly expanded to the outside, so the conclusion still needs a multi-center, large-sample, prospective randomized controlled study to further verify.

5. Conclusion

In this study, the mortality of patients in the medication group was much higher than that in the surgical repair group and percutaneous TCC group. Moreover, we found that whether combined with cardiogenic shock, NT-pro BNP level, EuroSCORE II score and treatment mode were independently associated with long-term mortality in patients with VSR. From the perspective of postoperative characteristics, surgical repair and percutaneous TCC have their own advantages and disadvantages, which still need to be further explored by multi center and large sample research. EuroSCORE II score has a good ability to predict the long-term mortality of VSR patients, so it can be considered to slightly modify the score content to expand the scope of application of EuroSCORE II. Clinically, it is still necessary to explore more appropriate treatment methods and

operation timing to improve the prognosis of VSR patients and reduce mortality.

6. List of abbreviations

VSR: Ventricular septal rupture; AMI: Acute myocardial infarction; EuroSCORE II: European Heart Surgery Risk Assessment System II; MACEs: Major adverse cardiac events; TCC: Transcatheter closure; STEMI: ST-elevation myocardial infarction; ACCF/AHA: American College of Cardiology Foundation/American Heart Association; ESC: European Society of Cardiology; TTE: Transthoracic echocardiogram; SOFA: Sequential Organ Failure Assessment; LM: Left main; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary arteries; LVEF: Left ventricle ejection fraction; LVEDD: Left ventricular end-diastolic dimension; PAP: Pulmonary artery pressure; SurCOP: Surgical repair combining an occluder and a patch; CABG: Coronary artery bypass graft; ICU: Intensive care unit; CRRT: Continuous renal replacement therapy; LCOS: Low cardiac output syndrome; PDA: Patent ductus arteriosus; SD: Standard deviation; ANOV A: One-way analysis of variance; WBC: White blood cells; ALT: Alanine transaminase; NT-pro BNP: N-terminal pro b-type natriuretic peptide; cTnI: Cardiac troponin I; ROC: Receiver operating characteristic; AUC: Area under the curve; CI: Confidence interval; HR: Hazard ratio; MODS: Multiple organ dysfunction syndrome; AST: aspartate transaminase; IABP: Intra-aortic balloon pump; CVC: Central venous catheter; CPB: Cardiopulmonary bypass support; OR: Odds ratio; STS: Society of Thoracic Surgeons; MCS: Mechanical circulatory support; AVB: Atrioventricular block; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; eGFR: estimated glomerular filtration rate; HbA1C: Hemoglobin A1C; SVG: Saphenous vein graft; LIMA: Left internal mammary artery.

7. Declarations

7.1. Ethics Approval and Consent to Participate

This study was approved by the institutional review boards of each participating institute, and informed consent was obtained before data collection. The study has therefore been performed in accordance with the Declaration of Helsinki (as revised in 2013).

7.2. Consent for Publication

All authors have read and approved the submission of the manuscript.

7.3. Availability of Data and Materials

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

7.4. Competing Interests

The authors declare that they have no competing interests.

7.5. Funding

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7.6. Authors' Contributions

XYZ, MD and XZ designed the research. SL, JT and ZY performed the research. MD and SL collected data. XZ and JT analyzed the data. MD drafted of the manuscript. XYZ, XZ, SL, JT and ZY reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Tables, figure and figure legend

Table 1. Clinical data of VSR patients stratified by different prognosis.

Clinical data	Grouping	Total number of cases (n=188)	Survival group (n=62)	Death group (n=126)	χ^2/t value/Z value	*P* value
Demographic characteristics						
Age, (years, $\bar{\chi}\pm s$)		66.2±9.1	64.7±8.6	66.9±9.3	1.529	0.128
Sex, [n (%)]	Male	97 (51.6%)	40 (64.5%)	57 (45.2%)	6.183	**0.013**
	Female	91 (48.4%)	22 (35.5%)	69 (54.8%)		
Age over 60, [n (%)]		148 (78.7%)	45 (72.6%)	103 (81.7%)	2.084	0.149
Comorbidities						
Smoking, [n (%)]		47 (25.0%)	20 (32.3%)	27 (21.4%)	2.599	0.107
Drinking, [n (%)]		30 (16.0%)	12 (19.4%)	18 (14.3%)	0.796	0.372
Hypertension, [n (%)]		101 (53.7%)	32 (51.6%)	69 (54.8%)	0.166	0.684
History of hypertension, (years, $\bar{\chi}\pm s$)		5.6±8.1	5.1±8.7	5.8±7.8	0.573	0.568
Diabetes, [n (%)]		62 (33.0%)	20 (32.3%)	42 (33.3%)	0.022	0.883
History of diabetes, (years, $\bar{\chi}\pm s$)		2.6±5.0	2.3±4.5	2.7±5.2	0.434	0.664
Hyperlipidemia, [n (%)]	With	20 (12.8%)	7 (13.0%)	13 (12.7%)	0.001	0.969
	Without	136 (87.2%)	47 (87.0%)	89 (87.3%)		
History of cerebral infarction, [n (%)]		32 (17.0%)	5 (8.1%)	27 (21.4%)	5.254	**0.022**
History of myocardial infarction, [n (%)]		17 (9.0%)	6 (9.7%)	11 (8.7%)	0.045	0.831
History of angioplasty, [n (%)]		8 (4.3%)	5 (8.1%)	3 (2.4%)	2.047	0.152
Prior fibrinolysis therapy, [n (%)]		14 (7.4%)	4 (6.5%)	10 (7.9%)	0.005	0.945
Pericardial effusion, [n (%)]		69 (36.7%)	24 (38.7%)	45 (35.7%)	0.160	0.689
Pleural effusion, [n (%)]		47 (25.0%)	17 (27.4%)	30 (23.8%)	0.289	0.591
III AVB, [n (%)]		4 (2.1%)	0 (0.0%)	4 (3.2%)	0.775	0.379
Malignant arrhythmia, [n (%)]		57 (30.3%)	5 (8.1%)	52 (41.3%)	21.686	**<0.001**

Cardiogenic shock, [n (%)]		47 (25.0%)	1 (1.6%)	46 (36.5%)	26.985	**<0.001**
Preoperative cardiac arrest, [n (%)]		12 (6.4%)	0 (0.0%)	12 (9.5%)	4.814	**0.028**
Right heart failure, [n (%)]		45 (23.9%)	10 (16.1%)	35 (27.8%)	3.097	0.078
Renal failure, [n (%)]		91 (48.4%)	15 (24.2%)	76 (60.3%)	21.712	**<0.001**
MODS, [n (%)]		23 (12.2%)	0 (0.0%)	23 (18.3%)	12.895	**<0.001**
The clinical situation						
Transferred from elsewhere, [n (%)]		96 (51.1%)	32 (51.6%)	64 (50.8%)	0.011	0.916
MI staging	Acute phase	181 (96.3%)	57 (91.9%)	124 (98.4%)	5.897	0.052
	Subacute phase	2 (1.1%)	2 (3.2%)	0 (0.0%)		
	Remote infarct	5 (2.7%)	3 (4.8%)	2 (1.6%)		
MI to VSR time, (d, $\bar{\chi}\pm s$)		6.2±6.9	8.0±7.9	5.3±6.1	-2.608	**0.010**
Killip classification, [n (%)]	1	1 (0.5%)	0 (0.0%)	1 (0.8%)	36.973	**<0.001**
	2	35 (18.6%)	23 (37.1%)	12 (9.5%)		
	3	27 (14.4%)	16 (25.8%)	11 (8.7%)		
	4	125 (66.5%)	23 (37.1%)	102 (81.0%)		
Laboratory data						
Lactic acid, [mmol/L, M (P25, P75)]		2.0 (1.4, 4.6)	1.4 (0.9, 1.9)	2.8 (1.7, 6.0)	-5.448	**<0.001**
WBC, [$*10^9$/L, M (P25, P75)]		11.4 (7.9, 15.1)	8.4 (6.4, 11.9)	13.7 (10.8, 16.7)	-5.907	**<0.001**
Hemoglobin, [g/L, M (P25, P75)]		126.0 (114.0, 137.0)	131.0 (122.2, 137.2)	122.1 (109.0, 137.0)	-2.293	**0.022**
Albumin, [g/L, M (P25, P75)]		36.0 (33.5, 38.9)	36.8 (33.7, 40.2)	35.4 (33.0, 38.4)	-2.050	**0.040**
Total bilirubin, [μmmol/L, M (P25, P75)]		15.0 (10.9, 27.5)	12.8 (9.1, 16.0)	20.7 (13.1, 30.0)	-3.712	**<0.001**
HDL, (mmol/L, $\bar{\chi}\pm s$)		0.9±0.3	0.9±0.3	0.9±0.4	0.804	0.423
LDL, (mmol/L, $\bar{\chi}\pm s$)		2.3±0.9	2.2±0.8	2.3±1.0	0.661	0.510
Uric acid, (μmol/L, $\bar{\chi}\pm s$)		448.8±260.9	347.6±179.4	499.0±280.4	3.780	**<0.001**
Creatinine, (μmol/L, $\bar{\chi}\pm s$)		151.8±139.6	93.2±37.5	180.6±161.1	4.140	**<0.001**
eGFR, (mL/min/1.73m^2, $\bar{\chi}\pm s$)		56.3±33.9	72.6±22.5	47.2±35.7	-4.820	**<0.001**

ALT, (U/L, $\bar{\chi}$±s)		514.6±1083.8	171.5±535.1	687.6±1240.5	3.078	**0.002**
AST, [U/L, M (P25, P75)]		91.0 (27.8, 557.8)	26.5 (29.0, 45.0)	202.0 (54.0, 5054.0)	-6.724	**<0.001**
Glucose, (mmol/L, $\bar{\chi}$±s)		9.9±8.7	7.9±3.8	10.9±10.2	2.220	**0.028**
HbA1C, (%, $\bar{\chi}$±s)		7.3±1.8	7.7±2.0	7.1±1.7	-1.552	0.123
NT-pro BNP, (pg/ml, $\bar{\chi}$±s)		12023.4±11136.1	5750.3±6615.8	15057.1±11620.3	5.715	**<0.001**
CTnI, (mmol/L, $\bar{\chi}$±s)		6.4±14.6	2.3±4.5	8.4±17.2	2.678	**0.008**
	Medication group	103 (54.8%)	6 (9.7%)	97 (77.0%)		
Therapy group	Percutaneous TCC group	34 (18.1%)	23 (37.1%)	11 (8.7%)	76.074	**<0.001**
	Surgical repair group	51 (27.1%)	33 (53.2%)	18 (14.3%)		
Therapeutic interventions						
ECMO support, [n (%)]		11 (5.9%)	2 (3.2%)	9 (7.1%)	0.556	0.456
IABP support, [n (%)]		50 (26.6%)	7 (11.3%)	43 (34.1%)	11.100	**0.001**
IABP difficult to offline, [n (%)]		40 (80.0%)	1 (14.3%)	39 (90.7%)	17.452	**<0.001**
CRRT, [n (%)]		22 (11.7%)	1 (1.6%)	21 (16.7%)	9.113	**0.003**
CVC, [n (%)]		84 (44.7%)	14 (22.6%)	70 (55.6%)	18.280	**<0.001**
Vasoactive drug, [n (%)]		188 (100.0%)	62 (100.0%)	126 (100.0%)	-	-
Severity score						
Gensini score, ($\bar{\chi}$±s)		66.4±39.2	63.6±37.3	69.2±41.3	0.671	0.504
SOFA score, ($\bar{\chi}$±s)		12.8±5.1	10.0±3.0	14.3±5.3	5.950	**<0.001**
EuroSCORE II, ($\bar{\chi}$±s)		14.8±2.7	12.5±2.0	16.0±2.3	9.910	**<0.001**

*****VSR, ventricular septal rupture; AVB, atrioventricular block; MODS, multiple organ dysfunction syndrome; AMI, acute myocardial infarction; WBC, white blood cells. HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; ALT, alanine transaminase; AST, aspartate transaminase; HbA1C, Hemoglobin A1C; NT-pro BNP, N-terminal pro b-type natriuretic peptide; CTnI, cardiac troponin I; TCC, transcatheter closure; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; CRRT, continuous renal replacement therapy; CVC, central venous catheter. SOFA, sequential organ failure assessment. P values in bold meant significantly different ($P<0.05$).

Table 2. Angiographic characteristics of VSR patients stratified by different prognosis.

Angiographic characteristics [n (%)]	Total number of cases （n=91）	Survival group（n=45）	Death group（n=46）	χ^2 value	*P* value
One-branch lesions	12 (13.2%)	8 (17.8%)	4 (8.7%)		
Two-branch lesions	27 (29.7%)	11 (24.4%)	16 (34.8%)	2.249	0.325
Three-branch lesions	52 (57.1%)	26 (57.8%)	26 (56.5%)		
LM	8 (8.8%)	3 (37.5%)	26 (62.5%)	0.114	0.736
LM+ three-branch lesions	6 (6.6%)	3 (50.0%)	3 (50.0%)	0.000	1.000
LAD	9 (9.9%)	5 (11.1%)	4 (8.7%)		
RCA	3 (3.3%)	3 (6.7%)	0 (0.0%)		
LCX	0 (0.0%)	0 (0.0%)	0 (0.0%)		
LAD+LCX	14 (15.4%)	7 (15.6%)	7 (15.2%)	5.919	0.314
LAD+RCA	11 (12.1%)	4 (8.9%)	7 (15.2%)		
LCX+RCA	2 (2.2%)	0 (0.0%)	2 (4.3%)		
LAD+RCA+LCX	52 (57.1%)	26 (57.8%)	26 (56.5%)		
100% occlusion	40 (44.0%)	18 (45.0%)	22 (55.0%)	0.566	0.452

*****VSR, ventricular septal rupture; LM, left main; LAD, left anterior descending branch; RCA, right coronary artery; LCX, left circumflex branch; 100% occlusion means complete occlusion in one or more of the three blood vessels.

Table 3. Echocardiogram outcomes of VSR patients stratified by different prognosis.

Echocardiogram outcomes	Grouping	Total number of cases (n=188)	Survival group (n=62)	Death group (n=126)	χ^2/t value/Z value	*P* value
MI territory, [n (%)]	Anterior	40 (23.7%)	18 (33.3%)	22 (19.1%)	6.426	0.093
	Extensive anterior	81 (47.9%)	20 (37.0%)	61 (53.0%)		
	Inferior	34 (20.1%)	13 (24.1%)	21 (18.3%)		
	Anterior septal	14 (8.3%)	3 (5.6%)	11 (9.6%)		
Multiple MI, [n (%)]	With	19 (10.1%)	8 (12.9%)	11 (8.7%)	0.797	0.372
	Without	169 (89.9%)	54 (87.1%)	115 (91.3%)		
Extensive anterior MI, [n (%)]	With	100 (53.2%)	28 (45.2%)	72 (57.1%)	2.396	0.122
	Without	88 (46.8%)	34 (54.8%)	54 (42.9%)		
LVEF, (%, $\bar{\chi}\pm s$)		49.2±10.0	51.2±9.8	48.2±10.0	-1.979	**0.049**
LVEDD, (mm, $\bar{\chi}\pm s$)		52.6±6.7	53.3±6.4	52.0±6.9	-0.911	0.365
Maximum rupture size, [mm, M (P25, P75)]		8 (5, 11)	7.0 (5.4, 11.8)	8.0 (5.0, 11.3)	-0.036	0.972
Multiple VSR, [n (%)]		9 (4.8%)	4 (6.5%)	5 (4.0%)	0.149	0.699
Combined with ventricular aneurysm, [n (%)]		94 (50.0%)	36 (58.1%)	58 (46.0%)	2.407	0.121
PAP over 60, [n (%)]		15 (8.0%)	8 (12.9%)	7 (5.6%)	2.137	0.080
VSR location, [n (%)]	Apical	108 (57.4%)	32 (51.6%)	76 (60.3%)	5.595	0.109
	Anterior	50 (26.6%)	15 (24.2%)	35 (27.8%)		
	Posterior	29 (15.4%)	15 (24.2%)	14 (11.1%)		
	Anterior+ posterior	1 (0.5%)	0 (0.0%)	1 (0.8%)		
Posterior rupture, [n (%)]	With	30 (16.0%)	15 (24.2%)	15 (11.9%)	4.679	**0.031**
	Without	158 (84.0%)	47 (75.8%)	111 (88.1%)		

*VSR, ventricular septal rupture; MI, myocardial infarction; LVEF, left ventricle ejection fraction; LVEDD, left ventricular end-diastolic dimension; PAP, Pulmonary artery pressure; MI territory refers to the location classification of one-site MI. P values in bold meant significantly different ($P<0.05$).

Table 4. Intraoperative characteristics of VSR patients in surgical repair group. (n=51)

Intraoperative characteristics	Grouping	Total number of cases (n=51)	Survival group (n=33)	Death group (n=18)	χ^2/t value	*P* value
Surgical status, [n (%)]	Emergency operation	3 (5.9%)	0 (0.0%)	3 (16.7%)	5.844	**0.039**
	Elective operation	48 (94.1%)	33 (100.0%)	15 (83.3%)		
Operation consuming time, (h, $\bar{\chi}$±s)		4.4±1.2	4.2±1.2	4.8±1.3	1.475	0.147
Surgical incision, [n (%)]	Ventricular aneurysm	43 (89.6%)	28 (90.3%)	15 (88.2%)	2.391	0.813
	Left ventricular	1 (2.1%)	1 (3.2%)	0 (0.0%)		
	Right atrium	3 (6.3%)	2 (6.5%)	1 (5.9%)		
	Aortic root	1 (2.1%)	0 (0.0%)	1 (5.9%)		
Surgical repair method, [n (%)]	Direct suture	5 (10.4%)	4 (12.9%)	1 (5.9%)	0.530	0.825
	Patch	27 (56.3%)	17 (54.8%)	10 (58.8%)		
	SurCOP	16 (33.3%)	10 (32.3%)	6 (35.3%)		
Concomitant CABG, [n (%)]		28 (58.3%)	20 (64.5%)	8 (47.1%)	1.377	0.241
Number of graft vessels, [n (%)]	1	18 (64.3%)	13 (61.9%)	5 (71.4%)	0.207	0.649
	2	10 (35.7%)	8 (38.1%)	2 (28.6%)		
Type of graft vessels, [n (%)]	SVG	19 (67.9%)	13 (61.9%)	6 (85.7%)	1.081	0.794
	LIMA	2 (7.1%)	2 (9.5%)	0 (0.0%)		
	SVG+LIMA	7 (25.0%)	6 (28.6%)	1 (14.3%)		
Concomitant ventricular aneurysm resection, [n (%)]		33 (68.8%)	22 (71.0%)	11 (64.7%)	0.200	0.654
Concomitant bicuspid annuloplasty, [n (%)]		3 (6.3%)	2 (6.5%)	1 (5.9%)	0.000	1.000
Concomitant tricuspid annuloplasty, [n (%)]		7 (14.6%)	6 (19.4%)	1 (5.9%)	0.701	0.402

*VSR, ventricular septal rupture; SurCOP, surgical repair combining an occluder and a patch; CABG, coronary artery bypass grafting; SVG, saphenous vein graft; LIMA, left internal mammary artery. *P* values in bold meant significantly different ($P<0.05$).

Table 5. Comparison of postoperative characteristics of VSR patients between surgical repair group and percutaneous TCC group. (n=85)

Postoperative characteristics	Grouping	Total number of cases (n=85)	Percutaneous TCC group (n=34)	Surgical repair group (n=51)	χ^2/t value/Z value	*P* value
Surgical status, [n (%)]	Emergency operation	4 (4.7%)	1 (2.9%)	3 (5.9%)	0.011	0.917
	Elective operation	81 (95.3%)	48 (94.1%)	33 (97.1%)		
Repair failure, [n (%)]		5 (5.9%)	4 (11.8%)	1 (2.0%)	1.992	0.158
Ventilator usage time, [h, M (P25, P75)]		22.7 (0.0, 52.9)	0.0 (0.0, 16.8)	37.9 (20.1, 62.0)	-5.058	**<0.001**
Hospital stay, (d, $\bar{\chi}\pm s$)		27.5±15.2	22.0±9.8	31.1±17.0	-2.804	**0.006**
ICU stay, (d, $\bar{\chi}\pm s$)		8.6±10.3	10.6±11.1	7.3±9.6	1.465	0.147
Post-operative residual shunt, [n (%)]		31 (37.8%)	19 (57.6%)	12 (24.5%)	9.181	**0.002**
Postoperative CRRT, [n (%)]		15 (18.5%)	4 (12.1%)	11 (22.9%)	1.510	0.219
Postoperative hemolysis, [n (%)]		38 (46.9%)	8 (24.2%)	30 (62.5%)	11.493	**0.001**
LCOS, [n (%)]		29 (35.8%)	10 (30.3%)	19 (39.6%)	0.733	0.392
EuroSCORE II, ($\bar{\chi}\pm s$)		13.7±2.6	13.9±2.4	13.5±2.7	0.762	0.448
Readmission, [n (%)]		23 (27.1%)	15 (44.1%)	8 (15.7%)	8.355	**0.004**
30-day mortality, [n (%)]		24 (28.2%)	10 (29.4%)	14 (27.5%)	0.039	0.844
MACEs, [n (%)]		51 (60.0%)	26 (76.5%)	25 (49.0%)	6.405	**0.011**
Overall mortality, [n (%)]		29 (34.1%)	11 (32.4%)	18 (35.3%)	0.079	0.779

*****VSR, ventricular septal rupture; TCC, transcatheter closure; ICU, intensive care unit; CRRT, continuous renal replacement therapy; LCOS, low cardiac output syndrome; MACE, major adverse cardiac events. *P* values in bold meant significantly different ($P<0.05$).

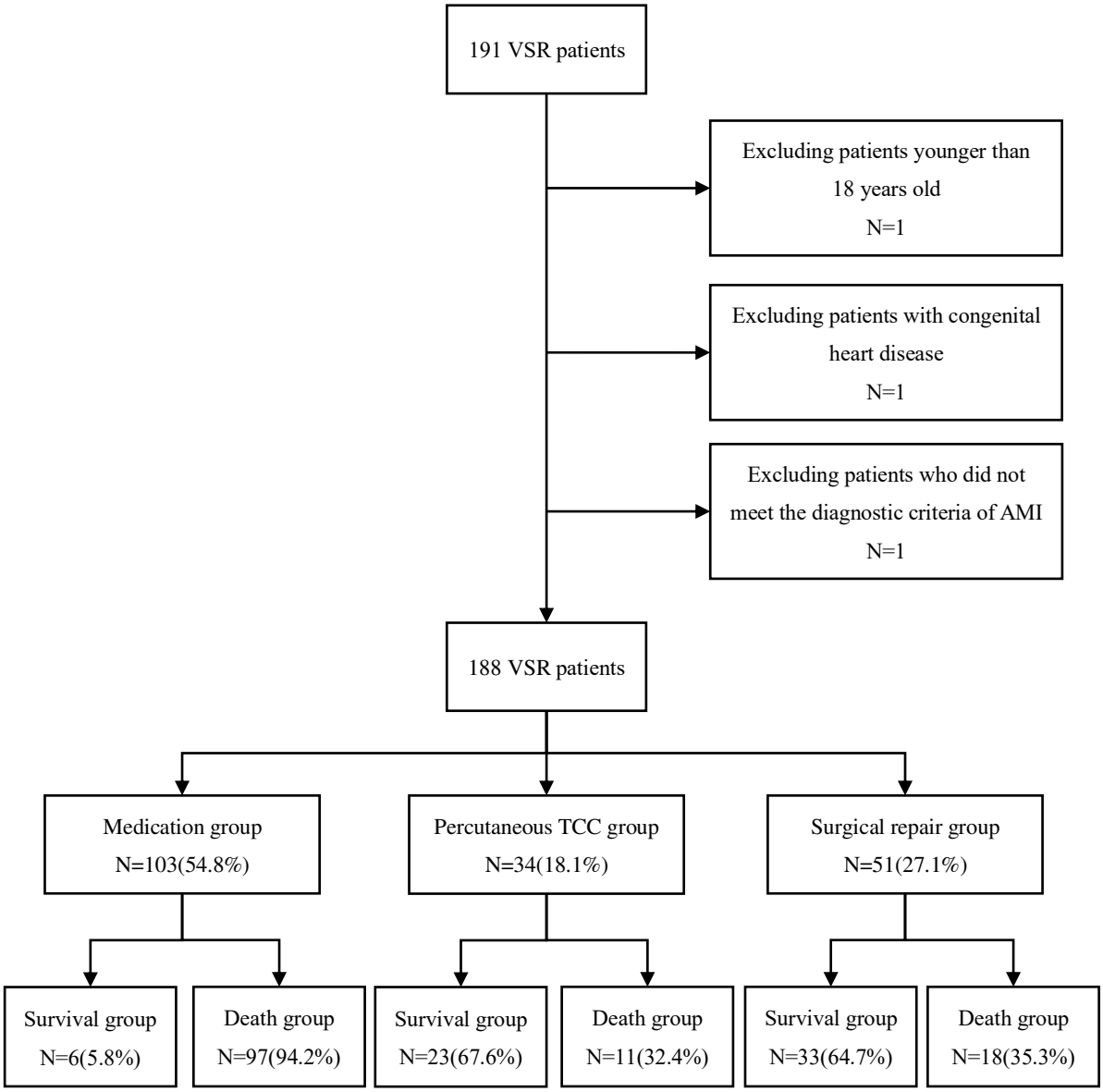


Fig 1. Flow diagram of patient inclusion and exclusion. VSR, ventricular septal rupture; AMI, acute myocardial infarction; TCC, transcatheter closure.

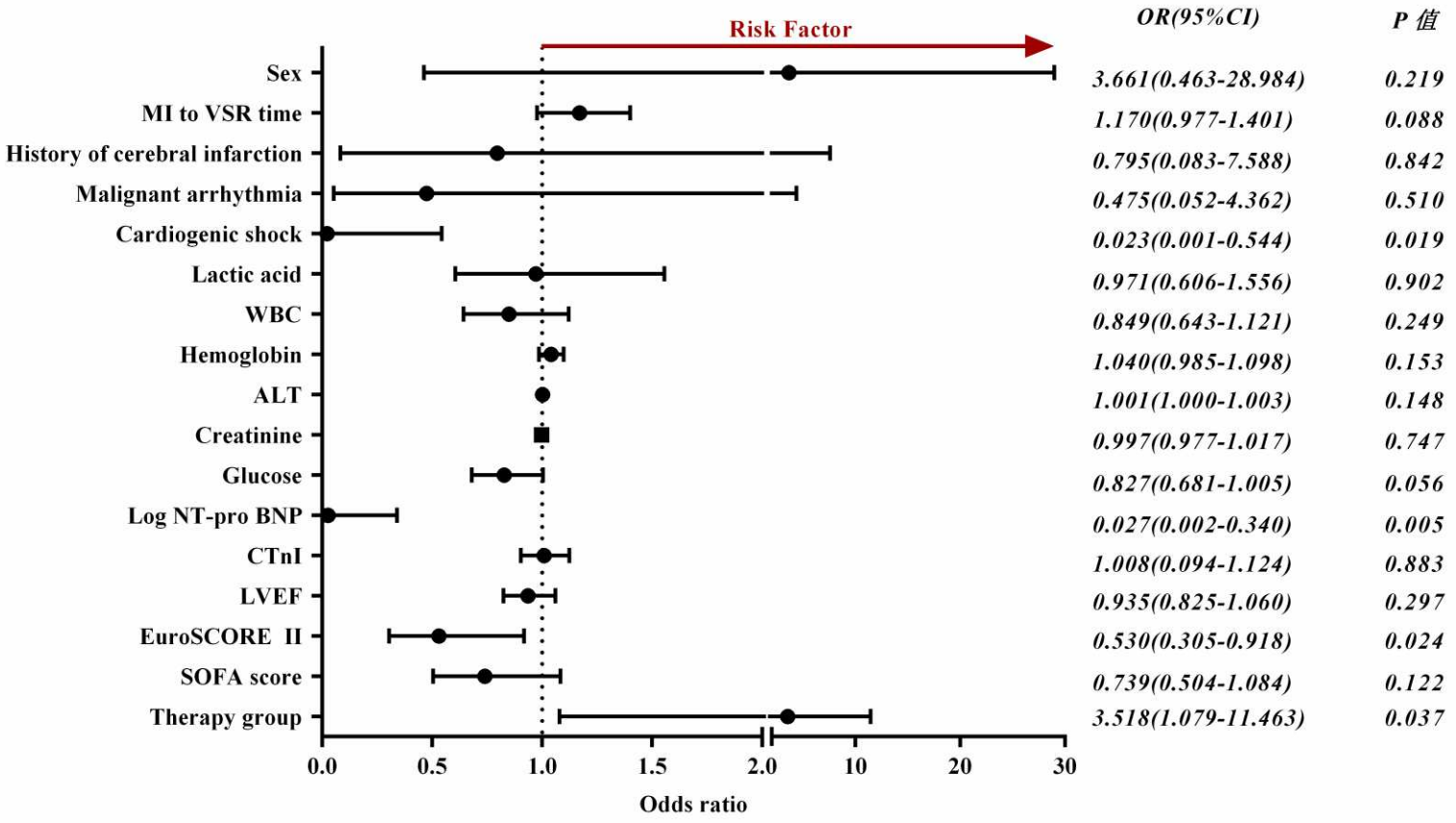
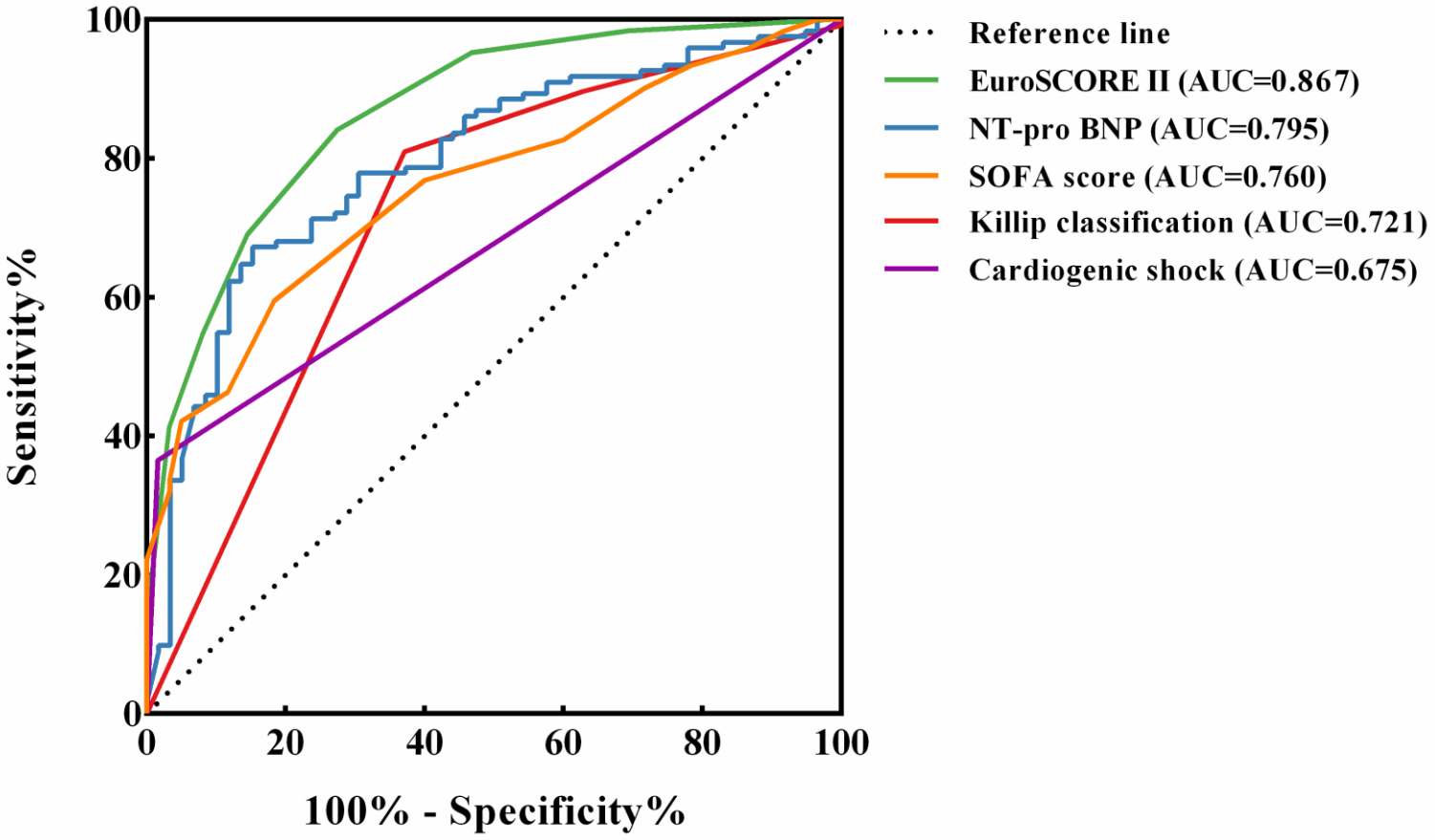


Fig 2. Forest plot depicts factors influencing the long-term prognosis of patients with VSR. OR, odds ratio; CI, confidence interval; MI, myocardial infarction; VSR, ventricular septal rupture; WBC, white blood cells; ALT, alanine transaminase; NT-pro BNP, n-terminal pro b-type natriuretic peptide; CTnI, cardiac troponin I; LVEF, left ventricle ejection fraction; SOFA, sequential organ failure assessment.



The following are the details of the five ROC curves:

EuroSCORE II: Cut-off value=14; AUC=0.867(95%CI: 0.813-0.921, $P<0.001$); Sensitivity: 84.1%; Specificity: 72.6%

NT-pro BNP: Cut-off value=8091; AUC=0.795(95%CI: 0.726-0.863, $P<0.001$); Sensitivity: 67.2%; Specificity: 84.7%

SOFA score: Cut-off value=13; AUC=0.760(95%CI: 0.690-0.829, $P<0.001$); Sensitivity: 59.5%; Specificity: 81.7%

Killip classification: AUC=0.721(95%CI: 0.639-0.802, $P<0.001$); Sensitivity: 81.0%; Specificity: 62.9%

Cardiogenic shock: AUC=0.675(95%CI: 0.599-0.750, $P<0.001$); Sensitivity: 36.5%; Specificity: 98.4%

Fig 3. ROC curves of EuroSCORE II, NT-pro BNP, SOFA score, Killip classification and Cardiogenic shock. ROC, receiver operating characteristic; AUC, area under curve ROC; CI, confidence interval; NT-pro BNP, n-terminal pro b-type natriuretic peptide; SOFA, sequential organ failure assessment.

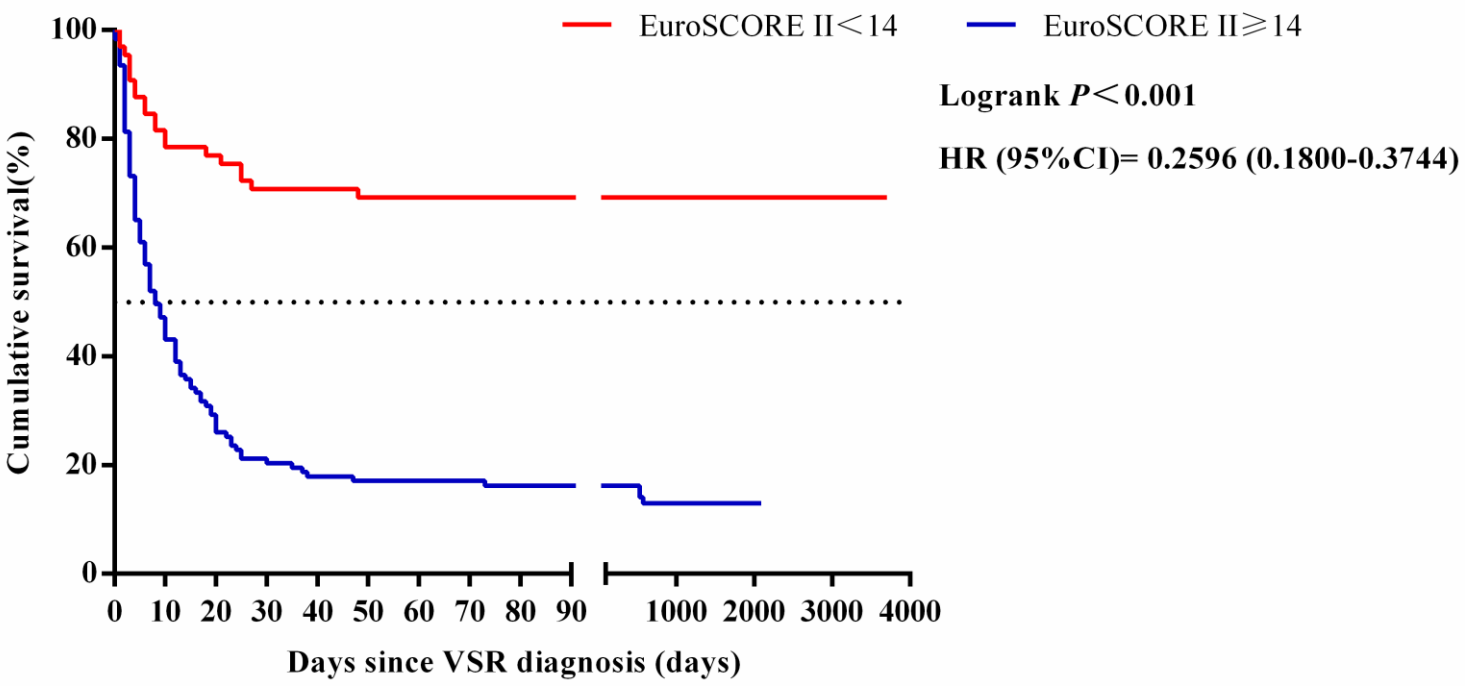


Fig 4. Relationships between the EuroSCORE II scores and 10-year mortality in patients with VSR. HR, hazard ratio; CI, confidence interval; VSR, ventricular septal rupture.

Table 2. Comparison lipoprotein subfractions between patients with and without T2D

Variables	Total (n=920)	T2D (n=204)	Non-T2D (n=716)	*p*-value
HDL-C(mg/dl)				
Large HDL-C(mg/dl)	13.35±6.94	12.27±6.21	13.65±7.11	**0.005**
Intermediate HDL-C(mg/dl)	20.55±5.82	20.93±7.92	20.44±5.07	0.481
Small HDL-C(mg/dl)	8.21±3.05	8.93±3.79	8.01±2.77	**0.003**
Large HDL (%)	30.61±8.18	28.50±7.55	31.21±8.26	**<0.001**
Intermediate HDL (%)	49.28±4.88	49.69±4.72	49.17±4.92	0.148
Small HDL (%)	20.02±6.22	21.51±6.21	19.59±6.17	**<0.001**
LDL-C(mg/dl)				
Large LDL-C(mg/dl)	27.01±9.50	26.51±9.26	27.15±9.57	0.441
Intermediate LDL-C(mg/dl)	18.92±8.16	19.87±7.79	18.65±8.25	0.050
Small LDL-C(mg/dl)	7.44±7.53	9.10±9.43	6.97±6.83	**0.012**
Large LDL (%)	14.54±4.13	14.05±4.18	14.68±4.11	0.094
Intermediate LDL (%)	10.01±3.39	10.35±3.07	9.91±3.47	0.163
Small LDL (%)	3.85±3.65	4.52±4.27	3.65±3.43	**0.017**
Mean LDL particle size(Å)	266.89±5.27	265.82±6.04	267.20±4.98	**0.011**

*****The data shown are the mean ± SD or n (%).Bold values indicate statistical significance. T2D= type 2 diabetes; HDL-C= high-density lipoprotein cholesterol; LDL-C= low-density lipoprotein cholesterol.

Table 3. Contributors to T2D as assessed by logistic regression analysis

Variables	Univariate		Multivariate	
	***p*-value**	**95% CI**	***p*-value**	**95% CI**
FPG (mmol/l)	**<0.001**	2.876-4.366	**<0.001**	2.721-4.174
HbA1C (mmol/mol)	**<0.001**	13.024-31.865	**<0.001**	12.607-31.932
TG (mmol/l)	**0.001**	1.089-1.417	**0.019**	1.028-1.369
TC (mmol/l)	0.085	0.981-1.349	-	-
HDL-C (mmol/l)	0.374	0.501-1.296	-	-
LDL-C (mmol/l)	0.085	0.980-1.378	-	-
Large HDL-C (mg/dl)	**0.013**	0.943-0.993	0.122	0.948-1.006
Intermediate HDL-C (mg/dl)	0.293	0.988-1.040	-	-
Small HDL-C (mg/dl)	**<0.001**	1.044-1.151	**0.005**	1.023-1.135
Large HDL (%)	**<0.001**	0.937-0.977	**0.001**	0.938-0.983
Intermediate HDL (%)	0.173	0.990-1.057	-	-
Small HDL (%)	**<0.001**	1.025-1.077	**0.009**	1.009-1.067
Large LDL-C (mg/dl)	0.403	0.977-1.010	-	-
Intermediate LDL-C (mg/dl)	0.059	0.999-1.038	-	-
Small LDL-C (mg/dl)	**<0.001**	1.016-1.056	**0.014**	1.005-1.048
Large LDL (%)	0.057	0.928-1.001	-	-
Intermediate LDL (%)	0.101	0.992-1.090	-	-
Small LDL (%)	**0.003**	1.021-1.107	0.064	0.998-1.088
Mean LDL particle size (Å)	**0.001**	0.927-0.981	**0.040**	0.940-0.999

*****Binary logistic regression analyses were used. Bold values indicate statistical significance. The adjusting known confounders were including age, gender, BMI, smoking, family history of CAD, hypertension, CAD, CCB and ACEI/ARB. T2D= type 2 diabetes; FPG= fasting plasma glucose; HbA1C= hemoglobin A1C; TG= triglyceride; HDL-C= high-density lipoprotein cholesterol; LDL-C= low-density lipoprotein cholesterol; CCB= calcium channel blocker; ACEI= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blockers.

Table 4. Comparison of percentages of controlled and uncontrolled T2D between low- and high- lipoprotein subfractions groups according to median

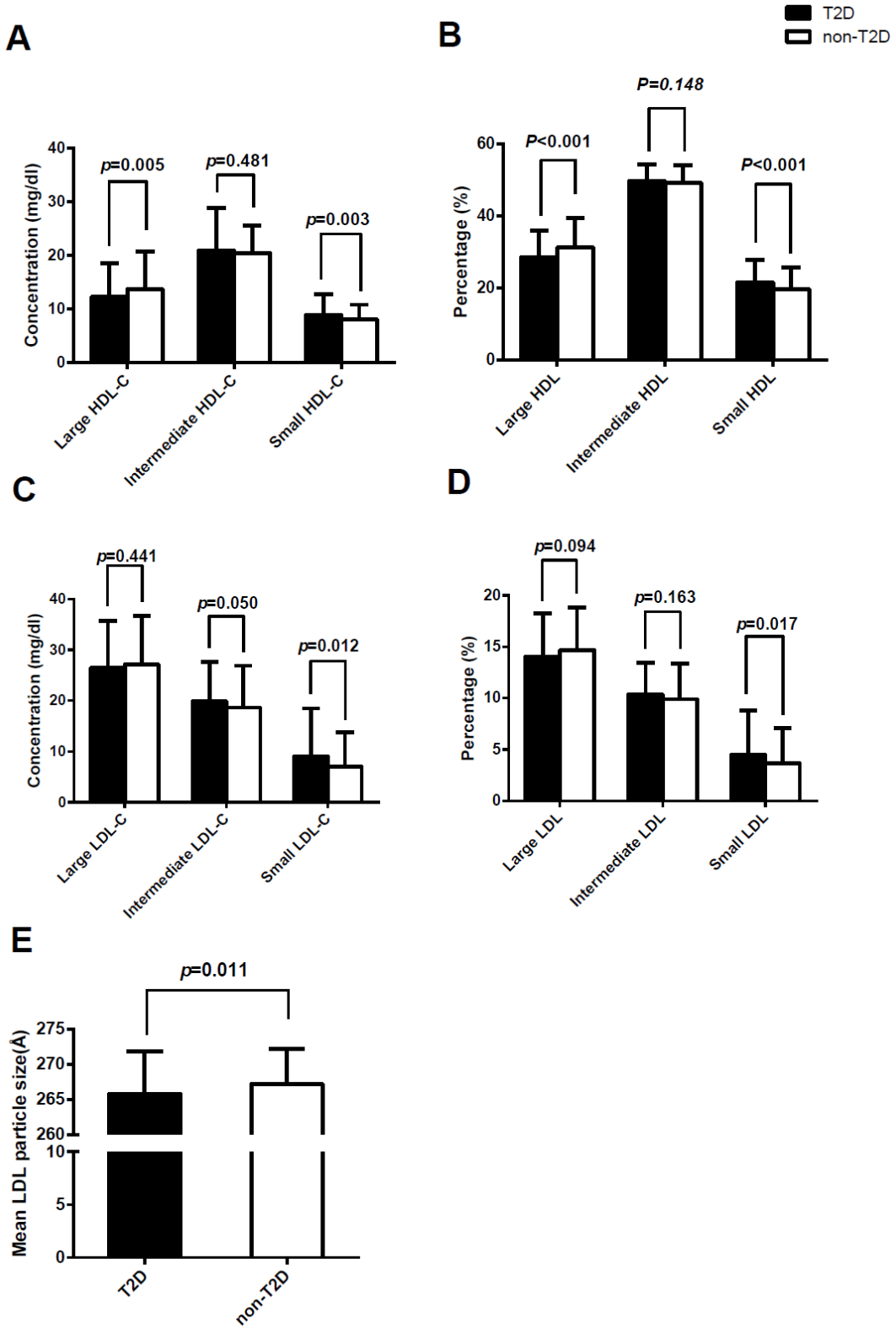
Variables	Controlled T2D (n=49)	Uncontrolled T2D (n=155)	*p*-value
Large HDL-C (3-10mg/dl, **n**=97**)**	20(20.6%)	77(79.4%)	0.326
Large HDL-C (11-44mg/dl, **n**=107**)**	29(27.1%)	78(72.9%)	
Small HDL-C (3-8mg/dl, **n**=104**)**	32(30.8%)	72(69.2%)	**0.023**
Small HDL-C (9-27mg/dl, **n**=100**)**	17(17.0%)	83(83.0%)	
Large HDL (10-27.9%, **n**=102**)**	22(21.6%)	80(78.4%)	0.512
Large HDL (28-57%, **n**=102**)**	27(26.5%)	75(73.5%)	
Small HDL (9.2-20.9%, **n**=96**)**	30(31.3%)	66(68.7%)	**0.032**
Small HDL (21-40.5%, **n**=108**)**	19(17.6%)	89(82.4%)	
Small LDL-C (0-5mg/dl, **n**=106**)**	30(28.3%)	76(71.7%)	0.144
Small LDL-C (6-54mg/dl, **n**=98**)**	19(19.4%)	79(80.6%)	
Small LDL (0-2.9%, **n**=102**)**	31(30.4%)	71(69.6%)	**0.049**
Small LDL (3-20.8%, **n**=102**)**	18(17.6%)	84(82.4%)	
Mean LDL particle size (239-267Å, **n**=103**)**	21(20.4%)	82(79.6%)	0.253
Mean LDL particle size (267.1-279.9Å, **n**=101**)**	28(27.7%)	73(72.3%)	

*****The data shown are the n (%).Bold values indicate statistical significance. T2D=type 2 diabetes; HDL-C=high-density lipoprotein cholesterol; LDL-C=low density lipoprotein-cholesterol.

Figure legends

Figure 1 (**A**) Concentrations of HDL-C subfractions, (**B**) percentages of HDL subfractions, (**C**) concentrations of LDL-C subfractions, (**D**) percentages of HDL subfractions, and (**E**) mean LDL particle size between type-2 diabetes (T2D) group (black) and non-T2D group (white). The values are shown as mean ±SD.

Figure 1


A
B
T2D
non-T2D
Concentration (mg/dl)
p=0.005
p=0.481
p=0.003
Large HDL-C
Intermediate HDL-C
Small HDL-C
Percentage (%)
P=0.148
P<0.001
P<0.001
Large HDL
Intermediate HDL
Small HDL
C
D
Concentration (mg/dl)
p=0.441
p=0.050
p=0.012
Large LDL-C
Intermediate LDL-C
Small LDL-C
Percentage (%)
p=0.094
p=0.163
p=0.017
Large LDL
Intermediate LDL
Small LDL
E
Mean LDL particle size(Å)
p=0.011
T2D
non-T2D