Original Article

The enlargement rate of ventricular septal rupture is a risk factor for 30-day mortality in patients with delayed surgery

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Background: Postinfarction ventricular septal rupture (VSR) is an uncommon but challenging mechanical complication for surgeons. This study analyzed the impacts of rupture size on surgical outcomes in patients with VSR.

Methods: During a 15-year period, from January 2006 to December 2020, 112 patients underwent repairs of postinfarction VSR. Patient clinical data, including angiographic and echocardiographic findings, operative procedures, early morbidity and mortality, and survival time were collated. Univariable and multivariable analyses were performed to identify the risk factors of 30-day mortality.

Results: The 30-day mortality rate was 7.1% for the whole cohort. The mean survival time estimate was 147.2 months [95% confidence interval (CI): 135.6 to 158.9 months], with a 3-year survival rate of 91.2% and a 5-year survival rate of 89.0%. Multivariable analysis revealed that rupture enlargement rate is an independent risk factor of 30-day mortality. The receiver operating characteristic (ROC) curve indicated that the rupture enlargement rate could predicted the 30-day mortality with high accuracy.

Conclusions: Delayed surgery may be considered for patients who respond well to aggressive treatment. The rupture enlargement rate is an independent risk factor for postoperative 30-day morality in patients with delayed VSR repair. Furthermore, the rupture enlargement rate has good predictive value for the prognosis of VSR patients.

Keywords: Ventricular septal rupture; ventricular septal perforation; risk factor analysis; delayed surgery

Submitted Nov 05, 2021. Accepted for publication Dec 15, 2021.
doi: 10.21037/atm-21-6243
View this article at: https://dx.doi.org/10.21037/atm-21-6243

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Introduction

Ventricular septal rupture (VSR) is a rare but fatal mechanical complication of acute myocardial infarction (AMI). Improved treatments for AMI have considerably reduced the mortality of AMI in the past decades, which has decreased the incidence of postinfarction VSR to 0.2% (1). However, the poor prognosis of VSR patients has not been improved significantly over the past decades, with an associated medical management mortality that ranges from 41% to 80% (1-4). Traditional opinion supports the immediate repair of a VSR as the rupture can expand abruptly, resulting in sudden hemodynamic collapse. The 2013 American Heart Association (AHA) guidelines for ST-segment elevation myocardial infarction (STEMI) recommended emergency surgical repair for all patients with VSR, even in hemodynamically stable patients (5). Although surgery is recognized as the most effective treatment for VSR, it carries an exceedingly high postoperative mortality of 42.9–80.5% within 7 days of VSR onset (1,6). However, due to an imperfect 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.

Delayed surgery has several advantages compared to immediate surgery. Studies have shown that the difficulty of the procedure, as well as the postoperative mortality and morbidity, all decline significantly in delayed surgery (7). With the increasing application of preoperative mechanical assistance, delayed surgery has gradually become acceptable in some clinical settings (8,9). In fact, the 2017 European Society of Cardiology (ESC) guidelines for STEMI suggested that delayed surgery could be considered for patients who respond well to aggressive treatment (10).

The risk factors for postoperative 30-day mortality include advanced age, female gender, renal dysfunction, cardiogenic shock, decreased ejection fraction (EF), three-branch lesions, and unstable status requiring preoperative intra-aortic balloon pump (IABP) (6). Other investigations have found that larger ruptures are more likely to cause preoperative cardiogenic shock (7), but no direct correlation between rupture size and postoperative mortality has been reported. To date, only a few studies have reported delayed surgery for VSR, with the majority being case reports and case series. Furthermore, there is a paucity of information regarding risk factors in delayed surgery for VSR. This study identified the independent risk factors of delayed VSR repair by reviewing the clinical data of VSR patients in our center, and analyzed the impacts of rupture size on the critical preoperative status and surgical outcomes.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-6243).

Methods

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This was a retrospective study and ethical approval was obtained from the ethics committee of Fuwai Hospital (No. 2021-1604). Individual consent for this retrospective analysis was waived.

Patients

A total of 112 consecutive patients with postinfarction VSR who underwent VSR repair between January 2006 and December 2020 in Fuwai Hospital were enrolled in this study. The average follow-up period was 65 months. The early outcomes were assessed by the postoperative 30-day mortality and morbidity. The primary endpoint was postoperative 30-day mortality, and the secondary endpoints included critical preoperative status and major adverse cardiovascular events (MACE) including cardiac death, myocardial infarction, and cerebral vascular accident, during follow-up. Clinical and follow-up data were collated from the hospital medical records and by phone consultations.

Diagnosis and definitions

VSR was diagnosed using the following criteria: (I) the appearance of rough blowing systolic murmurs between the third and fourth left ribs during post-AMI physical examinations; (II) loss of interventricular septum echo on echocardiography, and the presence of a left-to-right shunt; and (III) left ventriculography as indicated by left-to-right shunting of the contrast agent.

The maximum rupture size (Dmax) is defined as the preoperative maximum value of the defect diameter in mm, measured by transthoracic ultrasound. The minimum rupture size (Dmin) is defined as the preoperative minimum value of the defect diameter in mm, measured by transthoracic ultrasound. The rupture enlargement (ΔD) is calculated as follows: $\Delta D = Dmax - Dmin$. The rupture enlargement rate (ΔDR) is calculated as follows: $\Delta DR = \Delta D/T$, where T is the minimum time interval between

Dmax and Dmin in days (d).

The critical preoperative status is defined as preoperative severe hemodynamic instability requiring IABP implantation or emergency surgery.

Surgical intervention

An individualized delayed surgery strategy was adopted in our center. Hemodynamically unstable patients who showed little response to mechanical assistance would undergo emergency surgery with no delay. Patients who were stabilized by mechanical assistance or vasoactive agents would receive intensive care for at least 28 days before urgent surgery was performed. Stable patients who did not receive medication nor mechanical assistance would be strictly monitored in hospital for at least 28 days, followed by elective surgery.

With the exception of 5 cases of percutaneous septal closure, all other 107 cases underwent thoracotomy with cardiopulmonary bypass (CPB). Most patients underwent the classical patch procedure. The left ventricle was incised parallel to and 1–2 cm away from the anterior or posterior descending artery. Polyester patches were sutured to the uninfarcted or fibrotic ventricular septal tissue, as well as to the uninfarcted ventricle anterolateral wall tissue to isolate the infarcted myocardium from the left ventricle. The left ventricle incision was closed using the felt Sandwich method as previously described (11).

Statistical analysis

All statistical analyses were performed using the IBM SPSS 24.0 software. Statistical results are presented as median (Q1–Q3) or mean ± standard deviation. Baseline analysis among groups was performed with the chi-square (χ^2) tests or Fisher's exact tests for categorical data and the 2-tailed *t* test or the Mann-Whitney test for continuous data. Multivariable analysis was performed for variables that demonstrated statistical significance in the univariable analysis. Logistics regression was used for both univariate and multivariable analysis. Receiver operator characteristic curves (ROC curves) were used for the determination of the best cutoff point in predicting postoperative mortality. This cutoff point was determined by maximizing the Youden index (defined as sensitivity + specificity –1) of a ROC curve. Survival curves were plotted using the Kaplan-Meier method, and statistical differences were compared using a log-rank test. A P value less than 0.05 was considered statistically significant.

Results

Baseline characteristic

A total of 112 patients were included in this study and the baseline characteristics are listed in *Table 1*. There were 66 males and 46 females, with a mean age of 62.99 ±8.20 years. The medical history revealed that 68 patients had hypertension (60.71%), 45 had a history of smoking (40.18%), and 39 presented with diabetes mellitus (34.82%). The site of the infarction was anterior in 86 patients (76.79%) and posterior in 26 patients (23.21%). The ruptures were located at the anterior septum in 8 patients (7.14%), posterior septum in 23 patients (20.54%), and cardiac apex in 81 patients (72.32%) (*Table 2*).

Thrombolysis was performed in 15 cases (13.39%), and acute percutaneous coronary intervention (PCI) was performed in 30 patients (26.79%). The median time from AMI to the onset of VSR was 4 days, while the median time from VSR to surgical intervention was 53.5 days. Acute renal injury, defined as creatinine value greater than 200 mmol/L, was present in 22 patients. None of the patients had preoperative chronic renal failure that could confound this definition. All patients, except 5, had significant coronary lesions revealed by angiography. There was no significant difference in the frequency of 1-, 2-, and 3-vessel disease in the study cohort.

Early morbidity

A total of 44 patients (39.28%) required IABP to exit the operating room, while three patients (2.68%) needed intraoperative implantation of ventricular assistance devices. Reoperation due to deep sternal infection was performed in 6 patients (5.36%). A total of 10 patients (8.93%) received continuous renal replacement therapy due to postoperative renal failure. Postoperative echocardiography revealed the presence of postoperative shunts in 11 patients (9.82%), and only one patient underwent reoperation within 30 days after the primary procedure due to severe unstable circulation status.

The 30-day mortality

The 30-day mortality was 7.1% for the whole cohort, while the mortality was 100% when the operations were

Table 1 Patient data and risk factors of 30-day mortality

Variable	All (n=112)	Survivors (n=105)	Non-survivors (n=8)	P value
Demographics				
Age (y)	62.99±8.20	62.18±7.89	73.50±3.74	<0.001
≥60	80 (71.43%)	72 (69.23%)	8 (100.00%)	0.063
BMI	24.17±4.00	24.02±4.05	26.16±2.92	0.09
Male gender	66 (58.93%)	65 (62.50%)	1 (12.50%)	0.006
Co-morbidities				
Smoking history	45 (40.18%)	44 (42.31%)	1 (12.50%)	0.097
Alcohol drinking history	22 (19.64%)	21 (20.19%)	1 (12.50%)	0.598
Hypertension	68 (60.71%)	62 (59.62%)	6 (75.00%)	0.391
Diabetes	39 (34.82%)	34 (32.69%)	5 (62.50%)	0.088
Chronic obstructive pulmonary disease	1 (0.89%)	1 (0.96%)	0 (0.00%)	0.781
Previous cerebrovascular accident	7 (6.25%)	4 (3.85%)	3 (37.50%)	<0.001
Serum creatinine >200 μmol/L	22 (19.64%)	18 (17.31%)	4 (50.00%)	0.025
Arrhythmia				
Atrial fibrillation	4 (3.57%)	3 (2.88%)	1 (12.50%)	0.158
Ventricular tachycardia	2 (1.79%)	2 (1.92%)	0 (0.00%)	0.692
Atrioventricular block	3 (2.68%)	2 (1.92%)	1 (12.50%)	0.074
Acuity				
AMI-VSR time interval (d)	6.36±6.14	6.48±6.32	4.88±3.23	0.481
AMI-hospital time interval (d)	63.17±176.66	66.87±182.83	15.12±13.29	0.036
AMI-surgery time interval (d)	88.87±180.65	93.69±186.60	26.12±15.70	<0.001
Acute phase (≤7 d)	1 (0.89%)	0 (0.00%)	1 (12.50%)	<0.001
Healing phase (8–28 d)	14 (12.50%)	11 (10.58%)	3 (37.50%)	<0.001
Healed phase (>28 d)	97 (86.61%)	93 (89.42%)	4 (50.00%)	<0.001
Thrombolysis	15 (13.39%)	15 (14.42%)	0 (0.00%)	0.248
PCI	30 (26.79%)	29 (27.88%)	1 (12.50%)	0.344
Vasoconstrictor	71 (63.39%)	63 (60.58%)	8 (100.00%)	0.026
Preoperative IABP	46 (41.07%)	38 (36.54%)	8 (100.00%)	<0.001
Preoperative mechanical ventilation	2 (1.79%)	1 (0.96%)	1 (12.50%)	0.018
Critical preoperative status	49 (43.75%)	41 (39.42%)	8 (100.00%)	<0.001
EuroSCORE	13.20±4.61	12.63±4.24	20.50±2.56	<0.001

Table 1 (*continued*)

Table 1 (*continued*)

Variable	All (n=112)	Survivors (n=105)	Non-survivors (n=8)	P value
Angiography				0.91
Normal	5 (4.46%)	5 (4.81%)	0 (0.00%)	
One-branch lesions	23 (20.54%)	22 (21.15%)	1 (12.50%)	
Two-branch lesions	43 (38.39%)	39 (37.50%)	4 (50.00%)	
Three-branch lesions	35 (31.25%)	32 (30.77%)	3 (37.50%)	
Left main + two-branch lesions	1 (0.89%)	1 (0.96%)	0 (0.00%)	
Left main + three-branch lesions	5 (4.46%)	5 (4.81%)	0 (0.00%)	
Echocardiography				
Location of MI				0.456
Anterior wall	86 (76.79%)	79 (75.96%)	7 (87.50%)	
Posterior wall or inferior wall	26 (23.21%)	25 (24.04%)	1 (12.50%)	
Combined with ventricular aneurysm	79 (70.54%)	75 (72.12%)	4 (50.00%)	0.186
Location of rupture				0.261
Anterior septum	8 (7.14%)	7 (6.73%)	1 (12.50%)	
Posterior septum	23 (20.54%)	23 (22.12%)	0 (0.00%)	
Cardiac apex	81 (72.32%)	74 (71.15%)	7 (87.50%)	
Rupture size	13.20±5.05	13.07±5.11	14.88±4.09	0.185
Rupture enlargement	3.88±4.83	3.53±4.65	8.35± 5.10	0.006
Rupture enlargement rate	0.20±0.37	0.17±0.30	0.63±0.73	<0.001
LVEF	49.29±10.14	49.37±10.03	48.38±12.15	0.791
Surgical status				<0.001
Emergency operation	16 (14.29%)	11 (10.58%)	5 (62.50%)	
Urgent operation	57 (50.89%)	54 (51.92%)	3 (37.50%)	
Elective operation	39 (34.82%)	39 (37.50%)	0 (0.00%)	
Operative characteristics				
Repair method				0.546
Patch	80 (71.43%)	73 (70.19%)	7 (87.50%)	
Direct suture	17 (15.18%)	17 (16.35%)	0 (0.00%)	
Exclusion	10 (8.93%)	9 (8.65%)	1 (12.50%)	
Percutaneous closure	5 (4.46%)	5 (4.81%)	0 (0.00%)	
Cardiopulmonary bypass time (min)	114.63±56.06	109.14±47.11	186.00±104.48	<0.001
Aortic clamping time (min)	77.56±36.83	74.97±34.74	111.25±48.58	0.007
Concomitant CABG	66 (58.93%)	61 (58.65%)	5 (62.50%)	0.831
Concomitant mitral repair	5 (4.46%)	5 (4.81%)	0 (0.00%)	0.526

Table 1 (*continued*)

Table 1 (*continued*)

Variable	All (n=112)	Survivors (n=105)	Non-survivors (n=8)	P value
Postoperative outcomes				
Postoperative ventilation time (h)	58.80±95.88	43.12±50.57	262.62±238.78	<0.001
ICU stay (d)	6.95±7.01	6.04±5.00	18.75±15.50	<0.001
Postoperative IABP time	1.78±3.01	1.36±2.30	7.25±5.31	<0.001
Continuous renal replacement therapy	10 (8.93%)	7 (6.73%)	3 (37.50%)	0.003
Reoperation	6 (5.36%)	4 (3.85%)	2 (25.00%)	0.01
Postoperative shunt	11 (9.82%)	8 (7.69%)	3 (37.50%)	0.006
Postoperative cerebrovascular accident	1 (0.89%)	0 (0.00%)	1 (12.50%)	<0.001
Postoperative death	8 (7.14%)	0 (0.00%)	8 (100.00%)	<0.001

Values are presented as means ± standard deviation or the number of patients or fractions of patients. BMI, body mass index; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; IABP, intra-aortic balloon pump; VSR, ventricular septal rupture; EuroSCORE, European system for cardiac operative risk evaluation; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; ICU, intensive care unit.

performed in the acute phase [<7 days after AMI (12)], 21.4% in the healing phase (7–28 days), and 4.08% in the post-healing phase (29 days and beyond). Univariable analysis revealed that the significant risk factors of 30-day mortality were age, gender, infarction-surgery interval, previous cerebrovascular accident, ΔD, and ΔDR (*Table 3*). Multivariable analysis showed that the independent risk factors of 30-day mortality were female gender, older age, shorter infarction-surgery interval, previous cerebrovascular accident, lower ΔD, and higher ΔDR (*Table 4*).

The ROC curves for Dmax and ΔDR were plotted separately to evaluate their predictive power for 30-day mortality, yielding an area under the curve (AUC) of 0.641 and 0.863 , respectively (*Figure 1*). The results indicated that ΔDR predicted 30-day mortality with high accuracy.

The cut-off point was determined to be 0.205 mm/d by calculating the maximum of the Youden index. According to the cut-off point, the patients were divided into the low ΔDR group and the high ΔDR group. There were significant differences between the 2 groups in terms of preoperative IABP implantation, EuroSCORE, preoperative critical status, CPB time, aortic clamp time, postoperative ventilation time, intensive care unit (ICU) stay, reoperation, and 30-day mortality (*Table 5*).

Mid-term survival

There were 21 patients who were lost during follow-up due to changes in contact details. A total of 91 patients were followed-up for a median period of 65 months [interquartile range (IQR): 28–101 months]. During the follow-up period, 6 patients died due to MACE. The mean survival time estimate was 147.2 months [95% confidence interval (CI): 135.6 to 158.9 months], with a 3-year survival rate of 91.2% and a 5-year survival rate of 89.0%.

The median survival time estimates for the low ΔDR group and the high ΔDR group were 154.9 months (95% CI: 143.9 to 166.6 months) and 113.8 months (95% CI: 88.9 to 138.6 months), respectively. The survival curves of were plotted using the Kaplan-Meier method and log-rank test showed statistically significant differences between the low ΔDR group and the high ΔDR group (χ^2=5.775; P=0.016; *Figure 2*).

Discussion

Postinfarction VSD is an uncommon but challenging mechanical complication for surgeons. In the reperfusion era, approximately 0.2% of STEMI patients will be diagnosed with VSR (1,13-15). However, the reported postoperative mortality of emergency VSR repairs is no less than 30% (2,16-19), which represents one of the poorest prognoses in cardiac surgery. Therefore, it is important to identify patients with excessive risk in whom surgical intervention should be performed with caution.

It has been conventionally accepted that the average time

Table 2 Clinical characteristics according to the location of rupture

Variable	Anterior septum (n=8)	Posterior septum (n=23)	Cardiac apex (n=81)	P value
Acuity				
AMI-VSR time interval (d)	7.00±4.44	6.00±6.88	6.38±6.17	0.518
Critical preoperative status	5 (62.50%)	11 (47.83%)	33 (40.74%)	0.443
EuroSCORE	15.62±4.50	12.26±4.47	13.22±4.62	0.206
Echocardiography				
Location of MI				<0.001
Anterior wall	8 (100.00%)	5 (21.74%)	73 (90.12%)	
Posterior wall or inferior wall	0 (0.00%)	18 (78.26%)	8 (9.88%)	
Combined with ventricular aneurysm	5 (62.50%)	14 (60.87%)	60 (74.07%)	0.407
Rupture size	14.38±7.39	15.43±6.06	12.44±4.28	0.033
Operative characteristics				
Repair method				0.251
Patch	8 (100.00%)	14 (60.87%)	58 (71.60%)	
Direct suture	0 (0.00%)	5 (21.74%)	12 (14.81%)	
Exclusion	0 (0.00%)	4 (17.39%)	6 (7.41%)	
Percutaneous closure	0 (0.00%)	0 (0.00%)	5 (6.17%)	
Cardiopulmonary bypass time	136.88±31.02	130.57±51.77	107.91±58.06	0.022
Aortic clamping time	85.50±25.81	96.83±42.87	71.31±34.15	0.01
Concomitant CABG	3 (37.50%)	17 (73.91%)	46 (56.79%)	0.148
Concomitant mitral repair	0 (0.00%)	4 (17.39%)	1 (1.23%)	0.003
Postoperative outcomes				
Postoperative shunt	1 (12.50%)	2 (8.70%)	8 (9.88%)	0.874
Postoperative death	1 (12.50%)	0 (0.00%)	7 (8.64%)	0.261

AMI, acute myocardial infarction; VSR, ventricular septal rupture; EuroSCORE, European system for cardiac operative risk evaluation; MI, myocardial infarction; CABG, coronary artery bypass grafting.

between infarction and VSR decreases from 5 days to close to 1 day after the introduction of thrombolytic therapy (1,20-22). However, such a change was not supported by our finding, possibly because only 13.4% of the patients in this cohort had thrombolysis, and 26.8% underwent PCI. It is obvious that reperfusion therapy prevents the extensive myocardial necrosis typically associated with mechanical complications (1). However, patients who already have VSR would benefit little from reperfusion therapy, because their unstable status is related to left-to-right shunt rather than myocardial ischemia. Therefore, many cardiologists preferred IABP implantation rather than PCI or thrombolysis in patients with unstable VSR. Previous studies (6,7,23) support our findings with similar results.

In this study, a shorter infarction-surgery interval was found to be a significant risk factor for postoperative mortality, with operative mortality rates of 100%, 21.4%, and 4.08% in the acute, healing, and post-healing phases, respectively. This result was generally consistent with previous studies (6,24). The mortality of emergency VSR surgery was high due to the hemodynamic instability of patients in the acute phase of AMI, the fragile tissues surrounding the VSR, and hypoperfusion of systemic organs (20,24,25). However, as mechanical assisted implantations have become increasingly popular over the last decades, some patients can be stabilized by mechanical

Table 3 Univariable analysis for 30-day mortality by logistic regression analysis

Variable	β	OR	P
Male gender	−2.46	0.09	0.02
Age	0.29	1.34	0.00
BMI	0.20	1.22	0.12
Smoking history	−1.64	0.19	0.13
Alcohol drinking history	−0.57	0.56	0.60
Hypertension	0.71	2.03	0.40
Diabetes	1.23	3.43	0.10
AMI-surgery time interval (d)	−0.08	0.92	0.01
Thrombolysis	−18.79	0.00	1.00
PCI	−1.00	0.37	0.36
Chronic obstructive pulmonary disease	−18.65	0.00	1.00
Previous cerebrovascular accident	2.71	15.00	0.00
Atrial fibrillation	1.57	4.81	0.20
Ventricular tachycardia	−18.66	0.00	1.00
Vasoconstrictor	19.14	2.05E+08	1.00
Preoperative IABP	19.64	3.40E+08	1.00
Ccr	−0.04	0.96	0.06
Surgical status	–	–	0.03
Location of MI	0.80	2.22	0.47
LVA size	0.00	1.00	0.77
Rupture size	0.04	1.04	0.57
Rupture enlargement	0.14	1.15	0.15
Rupture enlargement rate	1.58	4.86	0.01
LVEF	−0.01	0.99	0.79

β, regression coefficient; OR, odds ratio; BMI, body mass index; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; Ccr, creatinine clearance rate; MI, myocardial infarction; LVA, left ventricular aneurysm.

assistance and safely pass the acute phase. 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 (6). With longer infarction-surgery intervals, consequent myocardial fibrosis would significantly reduce the difficulty of surgical procedures, which can result in good surgical outcomes. Therefore, patients who can be stabilized by mechanical assistance would benefit from the delayed surgery. Indeed, the 2017 ESC guidelines for STEMI suggested that delayed surgery should be considered for patients who respond well to aggressive treatment (10), and this is in agreement with our observations.

The delayed surgery strategy was adopted in our center, not only because of the substantial impact of shorter infarction-surgery intervals on the surgical outcomes (7), but also because only 22 cases (19.6%) were transported to our center within 7 days after infarction. The other 90 cases (80.4%) had already missed the acute phase at admission.

The multivariable analysis results showed that the AMI-surgery time interval was a powerful predictor of 30-day mortality, so the best surgical timing was as late as possible in theory. While things go different in fact. Unlimited delayed surgery would 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 studies and evidence are needed for verification.

This study demonstrated that older age and the female gender were predictors of 30-day mortality, and this was consistent with other reports (1,6,20). Although several investigations reported different results (23), possibly due to variations in the study cohort, it is generally accepted that older patients or female patients are more vulnerable, especially to diseases such as VSR.

This study demonstrated that the rupture enlargement rate was not only an independent risk factor, but also a strong predictor for postoperative mortality. Moreover, the results showed that the rupture enlargement was related to the critical preoperative status, as well as to prolonged postoperative ventilation time, length of ICU stay, and reoperation. These results have not been reported previously. The rupture enlargement rate has generally been overlooked in previous studies, probably because it is difficult to observe in the immediate surgery strategy. The VSR patients in previous studies received emergency operations early, and thus, there was insufficient time for surgeons to observe the changes in rupture size preoperatively. Clinically, the abrupt enlargement of ruptures is usually associated with reinfarction or reperfusion injury. After rupture enlargement, significantly increased shunts, and delays in fibrosis at defect edges may lead to hemodynamic instability, earlier timing of surgery,

Table 4 Multivariable analysis for 30-day mortality by logistic regression analysis

Variable	Multivariable analysis			Bootstrap correction	
	β	OR	P value	P value	95% CI of β
Rupture enlargement rate	4.136	62.563	0.207	0.003	–277.923 to 674.524
Rupture enlargement	–0.767	0.464	0.223	0.009	–74.946 to 13.672
Age	1.390	4.015	0.079	0.007	0.885 to 71.558
Male gender	–10.849	0.000	0.236	0.005	–575.630 to 17.965
AMI-surgery time interval	–0.180	0.835	0.244	0.005	–7.212 to 0.077
Previous cerebrovascular accident	11.454	94,289.562	0.080	0.006	4.773 to 417.923

Bootstrap was conducted with 1,000 replicates. β, regression coefficient; OR, odds ratio; 95% CI, 95% confidence interval; AMI, acute myocardial infarction.

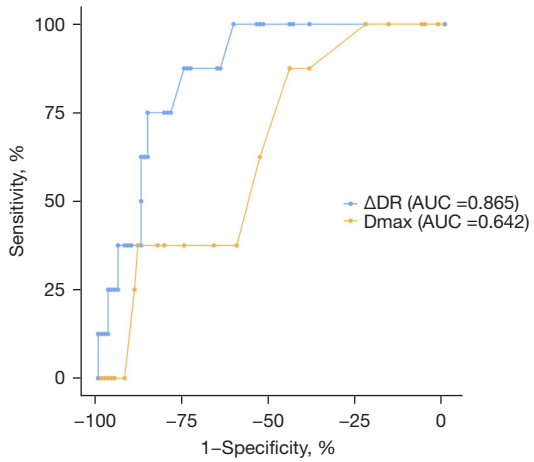

Figure 1 Receiver operating characteristic (ROC) curve assessing the predictive power of rupture size (Dmax) and rupture enlargement rate (ΔDR) in determining postoperative 30-day mortality. The plot shows that area under curve (AUC) is 0.865 for ΔDR and 0.642 for Dmax. Dmax is less accurate in predicting postoperative 30-day mortality as compared to ΔDR.

and increased difficulty of the operation. These factors all lead to poorer surgical outcomes, including increased postoperative mortality and morbidity.

Surprisingly, rupture enlargement was identified as a protective factor by multivariable analysis with an odds ratio (OR) value of 0.464, and this is in contrast to the clinical experience. Unstable patients tend to receive surgery sooner than stable patients, and thus, there is less time for ruptures to expand despite their higher rupture enlargement rate. In contrast, stable patients tend to have more time for adjustments before surgery, and thus, the rupture may expand slowly, resulting in greater rupture enlargements. As a result, the effect of rupture enlargement was corrected in multivariable analysis. Due to the small sample, our results only generated a research hypothesis that requires verification with further studies.

This study revealed a statistical significance in rupture size between the critical and noncritical groups, but similar results were not found between the survivors and non-survivors. Univariate regression also did not find an association between rupture size and postoperative mortality, and the ROC curve confirmed a poor predictive power of rupture size for postoperative mortality. The conventional opinion is that a larger rupture size or larger preoperative shunt can lead to cardiogenic shock (7,26), and this was verified by our data. The reason that rupture size affects the hemodynamic status is likely because rapid rupture enlargement leads to both bigger rupture size and sudden rise of shunts. However, most of the patients in this study with delayed surgery received preoperative mechanical assistance for weeks, and therefore, hemodynamic instability caused by large ruptures was likely to be corrected before the operation. Thus, the impact of rupture size on surgical outcome was eliminated by mechanical assistance in the delayed surgery strategy.

Although the ROC curves demonstrated a satisfactory predictive power of rupture enlargement rate on postoperative mortality, the median values of rupture enlargement rate for the non-survivor and survivor groups were 0.07 and 0.32 mm/d, respectively, and the cutoff point of the ROC curve was 0.205 mm/d, which is extremely difficult for transthoracic echocardiography to observe. More accurate examinations and further research are needed to explain the clinical significance of the rupture

Table 5 A comparison of the results between the low and high ΔDR groups

Variable	Low ΔDR group (n=80)	High ΔDR group (n=32)	P value
Acuity			
AMI-VSR time interval (d)	6.54±6.43	5.94±5.52	0.646
AMI-Hosp time interval (d)	78.78±206.45	24.16±30.57	<0.001
AMI-surgery time interval (d)	105.39±210.47	47.56±38.58	<0.001
Acute phase (≤7 d)	0 (0.00%)	1 (3.12%)	
Healing phase (8–28 d)	6 (7.50%)	8 (25.00%)	
Healed phase (>28 d)	74 (92.50%)	23 (71.88%)	
Critical preoperative status	27 (33.75%)	22 (68.75%)	<0.001
EuroSCORE	12.15±4.28	15.81±4.40	<0.001
Echocardiography			
Rupture size	11.50±3.82	17.44±5.30	<0.001
Rupture enlargement rate	0.06±0.07	0.56±0.53	<0.001
LVEF	49.79±10.05	48.06±10.41	0.418
Surgical status			0.001
Emergency operation	6 (7.50%)	10 (31.25%)	
Urgent operation	40 (50.00%)	17 (53.12%)	
Elective operation	34 (42.50%)	5 (15.62%)	
Operative characteristics			
Cardiopulmonary bypass time	108.30±54.63	130.47±57.31	0.058
Aortic clamping time	70.44±31.04	95.38±44.08	<0.001
Postoperative outcomes			
Postoperative ventilation time	47.85±74.85	86.19±132.50	0.021
ICU stay	5.94±5.90	9.47±8.85	0.003
Continuous renal replacement therapy	5 (6.25%)	5 (15.62%)	0.116
Reoperation	2 (2.50%)	4 (12.50%)	0.034
Postoperative shunt	8 (10.00%)	3 (9.38%)	0.92
Postoperative cerebrovascular accident	0 (0.00%)	1 (3.12%)	0.112
Postoperative death	2 (2.50%)	6 (18.75%)	0.003

ΔDR, rupture enlargement rate; AMI, acute myocardial infarction; VSR, ventricular septal rupture; EuroSCORE, European system for cardiac operative risk evaluation; LVEF, left ventricular ejection fraction; ICU, intensive care unit.

enlargement rate.

There were some limitations in this study. The retrospective design of this study may result in confounding factors, selection bias, and information bias. The small sample size resulted in the use of Bootstrap in the multivariable analysis to correct the result, and this may limit the reliability of the results. Future multi-center research with larger sample sizes are warranted to further

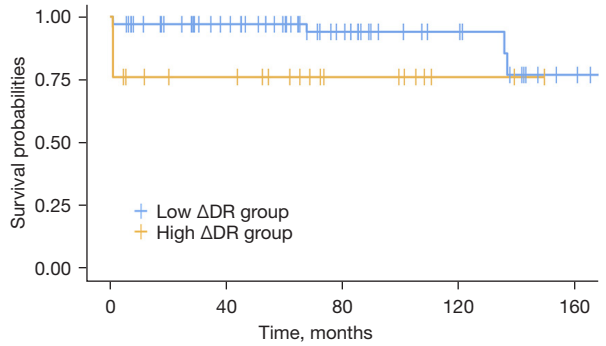

Figure 2 The survival curve for patients with low and high rupture enlargement rate (ΔDR). Kaplan-Meier overall survival curves shows a statistically significant difference between the two groups (log-rank χ^2=5.775; P=0.016).

confirm these results.

Conclusions

Rupture enlargement rate is an independent risk factor for postoperative 30-day morality in patients with delayed VSR repair and has good predictive power for the prognosis of VSR patients. Further research should be conducted to examine the clinical significance of the rupture enlargement rate.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-6243

Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-6243

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-6243). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This was a retrospective study and ethical approval was obtained from the ethics committee of Fuwai Hospital (No. 2021-1604). Individual consent for this retrospective analysis was waived.

References

1. Crenshaw BS, Granger CB, Birnbaum Y, et al. Risk factors, angiographic patterns, and outcomes in patients with ventricular septal defect complicating acute myocardial infarction. GUSTO-I (Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries) Trial Investigators. Circulation 2000;101:27-32.
2. Moreyra AE, Huang MS, Wilson AC, et al. Trends in incidence and mortality rates of ventricular septal rupture during acute myocardial infarction. Am J Cardiol 2010;106:1095-100.
3. López-Sendón J, Gurfinkel EP, Lopez de Sa E, et al. Factors related to heart rupture in acute coronary syndromes in the Global Registry of Acute Coronary Events. Eur Heart J 2010;31:1449-56.
4. French JK, Hellkamp AS, Armstrong PW, et al. Mechanical complications after percutaneous coronary intervention in ST-elevation myocardial infarction (from APEX-AMI). Am J Cardiol 2010;105:59-63.
5. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:529-55.
6. Arnaoutakis GJ, Zhao Y, George TJ, et al. Surgical repair of ventricular septal defect after myocardial infarction: outcomes from the Society of Thoracic Surgeons National Database. Ann Thorac Surg 2012;94:436-43; discussion

443-4.
7. Li H, Zhang S, Yu M, et al. Profile and Outcomes of Surgical Treatment for Ventricular Septal Rupture in Patients With Shock. Ann Thorac Surg 2019;108:1127-32.
8. Morimura H, Tabata M. Delayed surgery after mechanical circulatory support for ventricular septal rupture with cardiogenic shock. Interact Cardiovasc Thorac Surg 2020;31:868-73.
9. Furui M, Yoshida T, Kakii B, et al. Strategy of delayed surgery for ventricular septal perforation after acute myocardial infarction. J Cardiol 2018;71:488-93.
10. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
11. David TE, Dale L, Sun Z. Postinfarction ventricular septal rupture: repair by endocardial patch with infarct exclusion. J Thorac Cardiovasc Surg 1995;110:1315-22.
12. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. J Am Coll Cardiol 2007;50:2173-95.
13. Harikrishnan S, Tharakan J, Titus T, et al. Ventricular septal rupture following myocardial infarction: clinical, haemodynamic, angiographic profile and long-term outcome. Int J Cardiol 2007;120:279-80.
14. Nakatani D, Sato H, Kinjo K, et al. Effect of successful late reperfusion by primary coronary angioplasty on mechanical complications of acute myocardial infarction. Am J Cardiol 2003;92:785-8.
15. Yip HK, Fang CY, Tsai KT, et al. The potential impact of primary percutaneous coronary intervention on ventricular septal rupture complicating acute myocardial infarction. Chest 2004;125:1622-8.
16. Poulsen SH, Praestholm M, Munk K, et al. Ventricular septal rupture complicating acute myocardial infarction: clinical characteristics and contemporary outcome. Ann Thorac Surg 2008;85:1591-6.
17. Deja MA, Szostek J, Widenka K, et al. Post infarction ventricular septal defect - can we do better? Eur J Cardiothorac Surg 2000;18:194-201.
18. Jeppsson A, Liden H, Johnsson P, et al. Surgical repair of post infarction ventricular septal defects: a national experience. Eur J Cardiothorac Surg 2005;27:216-21.
19. Mantovani V, Mariscalco G, Leva C, et al. Surgical repair of post-infarction ventricular septal defect: 19 years of experience. Int J Cardiol 2006;108:202-6.
20. Menon V, Webb JG, Hillis LD, et al. Outcome and profile of ventricular septal rupture with cardiogenic shock after myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK? J Am Coll Cardiol 2000;36:1110-6.
21. Birnbaum Y, Fishbein MC, Blanche C, et al. Ventricular septal rupture after acute myocardial infarction. N Engl J Med 2002;347:1426-32.
22. Murday A. Optimal management of acute ventricular septal rupture. Heart 2003;89:1462-6.
23. Lundblad R, Abdelnoor M, Geiran OR, et al. Surgical repair of postinfarction ventricular septal rupture: risk factors of early and late death. J Thorac Cardiovasc Surg 2009;137:862-8.
24. Labrousse L, Choukroun E, Chevalier JM, et al. Surgery for post infarction ventricular septal defect (VSD): risk factors for hospital death and long term results. Eur J Cardiothorac Surg 2002;21:725-31; discussion 731-2.
25. Rob D, Špunda R, Lindner J, et al. A rationale for early extracorporeal membrane oxygenation in patients with postinfarction ventricular septal rupture complicated by cardiogenic shock. Eur J Heart Fail 2017;19 Suppl 2:97-103.
26. Jones BM, Kapadia SR, Smedira NG, et al. Ventricular septal rupture complicating acute myocardial infarction: a contemporary review. Eur Heart J 2014;35:2060-8.

(English Language Editor: J. Teoh)

Cite this article as: Ju F, Yuan X, Li B, Luo X, Wu H, Yang T, Sun H. The enlargement rate of ventricular septal rupture is a risk factor for 30-day mortality in patients with delayed surgery. Ann Transl Med 2021;9(24):1786. doi: 10.21037/atm-21-6243

