

Risk factors for cardiac rupture complicating myocardial infarction: a PRISMA meta-analysis and systematic review

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/jim-2018-000841>).

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Accepted 31 October 2018
Published Online First
28 November 2018

ABSTRACT

Cardiac rupture (CR) is a complication of acute myocardial infarction (AMI) that is associated with a high mortality rate. This study aimed to identify the risk factors for CR in patients with AMI. Medline, Cochrane, EMBASE, and Google Scholar databases were searched for relevant literature published through September 16, 2018. Eligible studies included patients with AMI and compared factors between patients with and without CR. Sixteen studies were identified and included in the meta-analysis. Results revealed that female gender (pooled OR=2.72, 95% CI 2.04 to 3.63, $p<0.001$), older age (pooled difference in means=6.91, 95% CI 4.20 to 9.62, $p<0.001$), infarction at left anterior descending coronary artery (LAD) (pooled OR=1.85, 95% CI 1.03 to 3.32, $p=0.039$), and anterior wall infarction (pooled OR=1.87, 95% CI 1.30 to 2.68, $p=0.001$) were associated with increased risk of CR, whereas history of MI, smoking, and multivessel disease were associated with reduced risk of CR. Patients treated with primary percutaneous coronary intervention (PCI) had reduced risk of CR, while patients who had received any thrombolysis had increased risk of CR. In conclusion, results of systematic review and meta-analysis of existing literature suggest that risk factors for CR in patients with AMI include female gender, older age, new-onset MI, non-smoking status, LAD infarction, anterior wall infarction, and single-vessel disease. Furthermore, treatment with primary PCI may help reduce the risk for CR, while thrombolysis might increase the risk for CR.

INTRODUCTION

Cardiac rupture (CR) is a complication of acute myocardial infarction (AMI) that can lead to poor prognosis, and is the second most frequent cause of death in patients with myocardial infarction (MI).^{1,2} CR-related death occurs in as many as 2% of patients with ST-elevation myocardial infarction (STEMI).² Due to its negative impact on morbidity and mortality, diagnosis and treatment of CR early in the disease progress are critical.³

CR is classified as ventricular septal rupture (VSR), free wall rupture (FWR), or papillary muscle rupture according to the site of occurrence. The diagnostic method of CR varies according to the occurrence site. Abnormal

Significance of this study

What is already known about this subject?

- Female patients have an increased risk of cardiac rupture (CR) compared with male patients.
- Older patients have a higher risk of CR compared with younger patients.
- Although hypertension is commonly considered a risk factor for CR, some studies reported that patients with hypertension have lower risk of CR than patients without hypertension.

What are the new findings?

- Patients with infarction involving the left anterior descending coronary artery or anterior wall had an increased risk of CR.
- History of myocardial infarction, smoking, and multivessel disease were associated with reduced risk of CR.
- Patients treated with primary percutaneous coronary intervention had a reduced risk of cardiac rupture, while patients treated with any thrombolysis had an increased risk of CR.

How might these results change the focus of research or clinical practice?

- These findings may aid in the identification of patients with acute myocardial infarction at increased risk of CR in future clinical practice, and further studies are warranted to investigate differences in risk factors for the various subtypes of CR, the impact of timing of reperfusion on CR risk, and biomarkers useful for the prediction of CR risk.

shunt flow at the interventricular septum on color Doppler echocardiography suggests VSR. FWR is diagnosed via pericardiocentesis followed by echocardiography, and is further classified as blow-out type or oozing type based on echocardiography, electrocardiography, and blood pressure findings. Echocardiography is the gold standard method for diagnosis of papillary muscle rupture.

Clinical symptoms of CR include recurrent chest pain, syncope, and distension of the



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To cite: Hao W, Lu S, Guo R, et al. *J Investig Med* 2019;**67**:720–728.

jugular vein, though sudden death from CR may occur in the absence of any symptoms or signs.⁴ Therefore, identification of patients at high risk for CR is important for early diagnosis and intervention. Several studies have revealed risk factors for CR, including female gender and older age.^{5–8} Results regarding the association between hypertension (HTN) and risk of CR have been conflicting.^{5,9} A comprehensive study for potential risk factors of CR in patients with AMI, in whom CR is particularly unfavorable, is lacking. In this study, we performed a meta-analysis to determine the risk factors for CR in patients with AMI.

MATERIALS AND METHODS

Search strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,¹⁰ the Medline, Cochrane, EMBASE, and Google Scholar databases were searched for literature published up to September 16, 2018 using combinations of the following keywords: cardiac rupture, ventricular septal rupture, left ventricular rupture, free wall rupture, papillary muscle rupture, ventricular pseudoaneurysm, ventricular septal defect, acute mitral regurgitation, myocardial infarction, predictive factors, and risk factors. References in relevant articles were hand-searched for additional eligible publications. The inclusion criteria were: (1) all included patients were diagnosed with AMI; (2) factors between CR and non-CR patients were compared; and (3) outcomes were reported according to studied risk factors. The exclusion criteria were: (1) letters, comments, editorials, proceeding, and personal communication; (2) non-comparative single-arm study design; (3) inclusion of patients without AMI; and (4) lack of quantitative outcomes.

Data extraction

Data extraction was performed independently by 2 reviewers. A third reviewer was consulted if there was any disagreement. Data on study design, demographic characteristics, medical history, treatments, and outcomes were extracted.

Quality assessment

Two independent reviewers assessed the quality of included studies using the Cochrane risk of bias assessment tool for non-randomized studies of interventions (ACROBAT-NRSI).¹¹ A third reviewer was consulted in case of disagreement.

Statistical analysis

The evaluated risk factors associated with CR complicating AMI were gender, age, medical history including HTN, diabetes mellitus, dyslipidemia, history of MI, history of angina and previous percutaneous coronary intervention (PCI), previous coronary artery bypass graft, smoking status, medication use including statin, β -blocker, ACE inhibitor (ACEI)/angiotensin receptor blocker (ARB), thrombolysis and dual antiplatelet treatment, vessel and site of infarction, and primary PCI. Risk factors were estimated by the difference in means or OR and their corresponding 95% CIs for each individual study as well as the pooled data. A χ^2 -based test of homogeneity was performed and

the inconsistency index (I^2) and Q statistics were determined. Studies were considered to be heterogeneous or highly heterogeneous if I^2 was $>50\%$ or $>75\%$, respectively. Studies were considered to be homogeneous if I^2 was $<25\%$. The random effects method was used to pool study findings since the effects, regardless of risk factor, originated from the same sample of studies. Pooled effects were calculated and a two-sided p value <0.05 was considered statistically significant. Sensitivity analysis was carried out using the leave-one-out approach to determine the robustness of the outcomes. Publication bias was assessed by constructing funnel plots via Egger's test. A symmetrical funnel-shaped distribution of data points with one-tailed significance level of $p>0.05$ indicated the absence of publication bias. If publication bias existed, adjusted effect sizes were calculated after consideration of publication bias using Duval and Tweedie's 'trim and fill' procedure.¹² All analyses were performed using Comprehensive Meta-Analysis statistical software, V.2.0 (Biostat, Englewood, NJ, USA).

RESULTS

Basic characteristics of patients in included studies

Keyword searches initially identified 900 articles, of which 819 were excluded after title and abstract screening. Full-text review of the remaining 81 articles was conducted, and 65 publications were further excluded due to the following reasons: lack of comparison; lack of outcome of interest; abstract only; inclusion of only patients with fatal MI; duplicated populations; presented as letter, editorial, or meta-analysis (figure 1).

Therefore, 16 studies met the eligibility criteria and were included in the systematic review and meta-analysis.^{1 5–9 13–22} All included studies were retrospective in design. The number of patients with MI included in each study ranged from 37 to 148,881 (total $n=242,618$). The characteristics and outcomes of patients in the included studies are summarized in table 1. Patients' age ranged from 61 to 78.3 years. The occurrence rate of CR ranged from 0.20% to 24.32%.

Meta-analysis

Results of meta-analysis for the association between female gender and the risk of CR are illustrated as a forest plot in figure 2A. There was high heterogeneity among the 16 studies (heterogeneity test: $Q=108.27$, $I^2=86.15\%$). The overall analysis revealed that female gender was significantly associated with increased risk of CR (pooled OR=2.72, 95% CI 2.04 to 3.63, $p<0.001$).

For evaluation of age as a risk factor of CR, Ruiz-Bailén *et al*⁹ were excluded as age was not reported in this study. The remaining 15 studies were highly heterogeneous (heterogeneity test: $Q=482.95$, $I^2=96.34\%$). The overall analysis revealed that older age was significantly associated with increased risk of CR (pooled difference in means=6.91, 95% CI 4.20 to 9.62, $p<0.001$, figure 2B).

The forest plot for HTN as a risk factor shows a relatively high level of heterogeneity among the 13 studies (heterogeneity test: $Q=142.29$, $I^2=91.96\%$), and the pooled data revealed that HTN was not associated with CR (pooled OR=1.16, 95% CI 0.73 to 1.84, $p=0.535$, figure 2C). Only 9 studies reported history of MI, and there

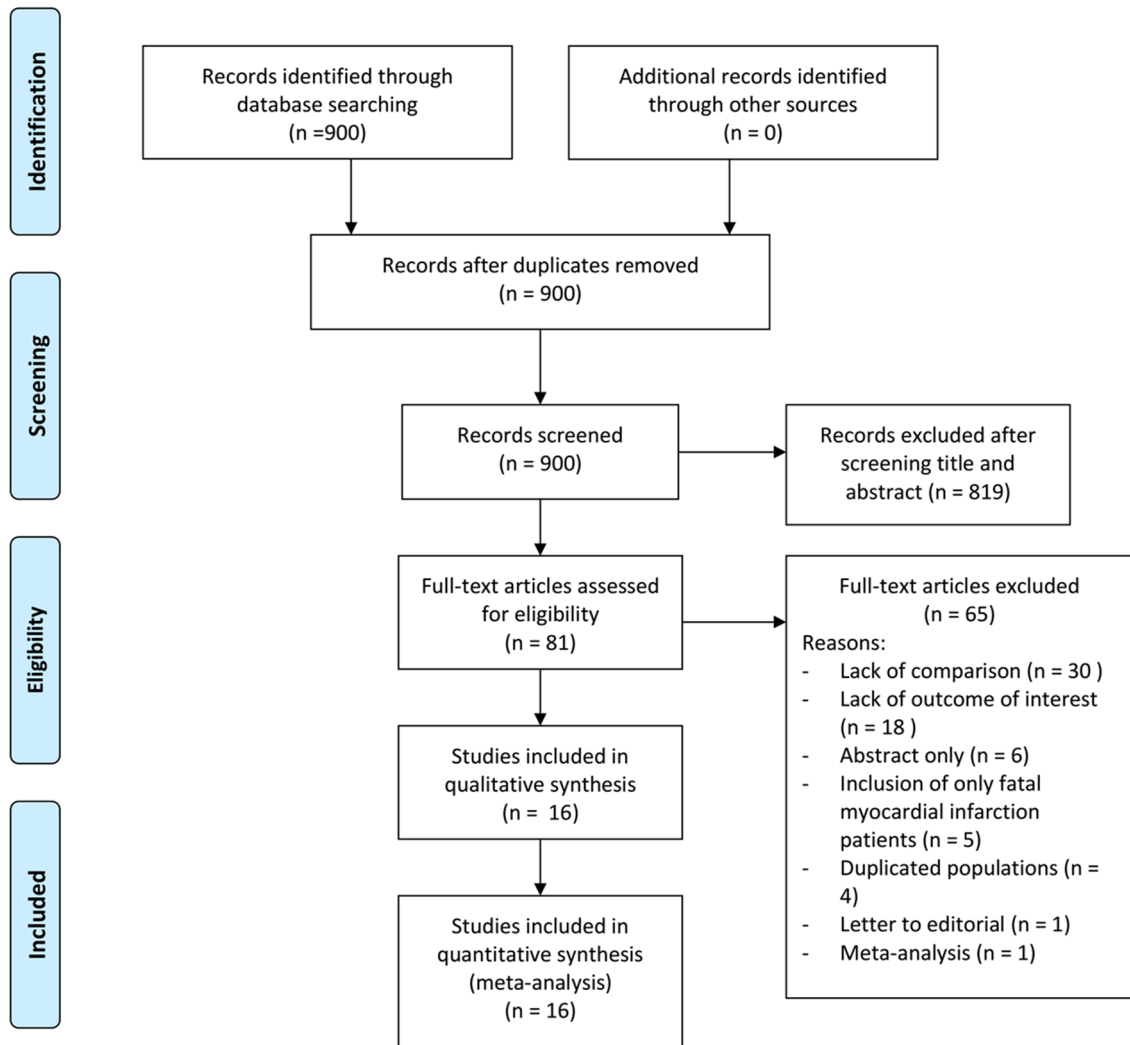


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

was no significant heterogeneity among the studies (heterogeneity test: $Q=12.52$, $I^2=36.08\%$). The overall analysis revealed that history of MI was significantly associated with reduced risk of CR (pooled OR=0.61, 95% CI 0.40 to 0.93, $p=0.021$, [figure 2D](#)).

A forest plot illustrating the association between infarction involving the left anterior descending coronary artery (LAD) and the risk of CR is given in [figure 3A](#). The overall analysis revealed that LAD involvement was associated with increased risk of CR (pooled OR=1.85, 95% CI 1.03 to 3.32, $p=0.039$); although the 9 studies included in the analysis were highly heterogeneous (heterogeneity test: $Q=39.70$, $I^2=79.85\%$). There was a high level of heterogeneity among the 10 studies that provided information on anterior wall infarction (heterogeneity test: $Q=58.09$, $I^2=84.51\%$). The overall analysis revealed that anterior wall infarction was significantly associated with increased risk of CR (pooled OR=1.87, 95% CI 1.30 to 2.68, $p=0.001$, [figure 3B](#)).

Moderate heterogeneity was found among the 8 studies that reported on the presence of multivessel disease (heterogeneity test: $Q=12.90$, $I^2=45.72\%$). Results of meta-analysis showed that patients with multivessel disease

had significantly reduced risk of CR (pooled OR=0.54, 95% CI 0.35 to 0.86, $p=0.009$, [figure 3C](#)).

In addition, patients with history of smoking (pooled OR=0.40, $p<0.001$), β -blocker usage (pooled OR=0.40, $p=0.021$), ACEI/ARB usage (pooled OR=0.62, $p=0.001$), infarction involving the right coronary artery (RCA) (pooled OR=0.66, $p=0.018$), and treatment with primary PCI (pooled OR=0.33, $p=0.001$) had significantly reduced risk of CR ([table 2](#)). However, patients with Killip class IV MI (pooled OR=10.14, $p<0.001$), left main (LM) coronary artery involvement (pooled OR=5.51, $p<0.001$), and treatment with thrombolysis (pooled OR=2.03, $p=0.002$) had significantly increased risk of CR ([table 2](#)).

Sensitivity analysis

Sensitivity analyses were performed using the leave-one-out approach in which the meta-analyses for female gender, age, HTN, history of MI, LAD involvement, anterior wall infarction, and multivessel disease were performed with each study removed in turn (online supplementary table 1). For female gender, age, HTN, and anterior wall infarction, the direction and magnitude of combined estimates did not

Table 1 Summary of basic characteristics and outcome of selected studies for meta-analysis

First author (yr)	Time	Group	Patients (n)	ST elevation (%)	Female (%)	Age (y)	HTN (%)	DM (%)	Dyslipidemia (%)	Smoking (%)	History of MI (%)
Chang ⁷ (2016)	1999–2013	FWR	24	100.0	29.2	72.8	50.0	45.8	12.5	25.0	NA
		Control	1521		23.8	63.1	53.6	38.5	42.5	42.1	NA
Nozoe ⁵ (2014)	2005–2011	LVR	36	88.9	44.4	74.6	30.6	22.2	NA	NA	0.0
		VSR	19	89.5	57.9	78.2	10.5	21.2	NA	NA	0.0
		FWR	17	88.2	29.4	70.6	52.9	23.5	NA	NA	0.0
		Control	1254	75.3	29.0	69.9	75.4	36.4	NA	NA	11.8
Qian ⁶ (2014)	2011–2013	CR	178	100.0	44.9	67	60.7	27.0	22.5	33.1	NA
		Control	9620		19.3	61	52.7	24.0	17.4	53.0	NA
Ledakowicz-Polak ²⁰ (2011)	2004–2006	VSR	13	100.0	69.2	72.1	76.9	53.9	NA	23.1	NA
		Control	1822		28.2	61.2	50.8	32.0	NA	56.0	NA
Ptaszyńska-Kopczyńska ⁸ (2011)	2000–2007	CR	23	100.0	47.8	66.3	NA	NA	NA	NA	NA
		Control	255		25.9	61.1	NA	NA	NA	NA	NA
French ²¹ (2010)	2004–2006	FWR	30	100	60.0	74	60.0	20.0	36.7	20.0	6.7
		PMR	15		40.0	68	40.0	13.3	20.0	33.3	13.3
		VSR	10		70.0	72	70.0	20.0	40.0	40.0	0.0
		Control	5693		22.8	61	49.4	15.9	38.0	43.2	12.1
Moreyra ¹⁰ (2010)	1990–2007	VSR	408	100.0	51.5	71	28.4	17.9	NA	NA	NA
		Control	148,473		38.5	67	45.6	24.0	NA	NA	NA
Ruiz-Bailén ⁹ (2010)	1996–2005	CR	477	NA	42.1	NA	52.2	27.7	23.7	36.5	8.0
		Control	16,338		24.3	NA	45.6	28.6	32.1	56.8	17.2
Rigatelli ¹⁵ (2008)	2005–2007	LVR	11	NA	81.8	77	NA	NA	NA	NA	NA
		Control	337		43.0	76	NA	NA	NA	NA	NA
Katayama ¹⁶ (2006)	NA	CR	11	NA	63.6	76	63.6	63.6	45.5	NA	18.2
		Control	422		32.0	69	56.0	33.0	42.9	NA	14.0
Okino ¹⁷ (2005)	1985–2003	FWR	24	NA	58.3	70.8	37.5	33.3	8.3	29.2	0.0
		Control	3042		27.3	66.1	45.3	29.7	22.0	45.9	10.0
Yip ¹⁸ (2004)	1993–2003	VSR	21	NA	76.2	74.1	81.0	28.6	38.1	9.5	9.5
		Control	1916		17.1	61.5	48.6	28.0	43.4	56.8	9.6
Solodky ¹⁴ (2001)	1996	CR	58	NA	48.3	71	53.4	29.3	NA	22.4	19.0
		Control	2319		24.9	62.3	40.7	24.6	NA	35.9	22.5
Crenshaw ²² (2000)	1990–1993	VSR	84	NA	57.1	72	57.1	21.4	NA	13.1	11.9
		Control	40,937		25.2	61	37.9	14.6	NA	42.7	16.4
Becker ¹ (1996)	1990	CR	870	NA	49.5	70.6	NA	NA	NA	NA	NA
		Control	6303		44.7	70.4	NA	NA	NA	NA	NA
Ueda ¹⁹ (1996)	1990–1995	CR	9	NA	22.2	67.5	88.9	NA	NA	NA	11.0
		Control	28		25.0	62.8	60.7	NA	NA	NA	0.0

CR, cardiac rupture; DM, diabetes mellitus; FWR, free wall rupture; HTN, hypertension; LVR, left ventricular rupture; MI, myocardial infarction; NA, not available; PMR, papillary muscle rupture; VSR, ventricular septal rupture.

vary markedly with the removal of individual studies, indicating that the meta-analysis was robust and the data were not overly influenced by any individual study.

Pooled OR of multivessel disease remained <1 after each study was removed in turn. Although the OR became non-significant (borderline p value) with the removal of Nozoe *et al*,⁵ all others remained significant, which indicates no obvious influence of any individual study on the pooled estimate. For history of MI, pooled OR remained <1 after sensitivity analysis, though removal of French *et al*²¹ and Crenshaw *et al*²² resulted in borderline non-significant p values. Removal of Ruiz-Bailén *et al*,⁹ however, resulted in a non-significant pooled OR, suggesting that the pooled estimates for history of MI might be affected by this individual study.

Likewise for infarction involving the LAD, pooled OR remained >1 after each study was removed, although p values became borderline non-significant with removal of Ptaszyńska-Kopczyńska *et al*⁸ and Katayama *et al*,¹⁶ and became non-significant with removal of Nozoe *et al*,⁵ Ledakowicz-Polak *et al*,²⁰ Yip *et al*,¹⁸ and Crenshaw *et al*.²² Therefore, pooled estimates for LAD involvement might be affected by these 4 studies (online supplementary table 1).

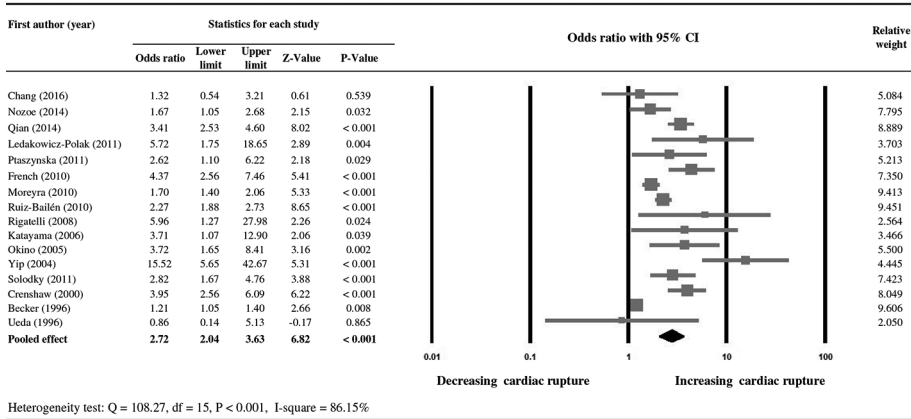
Publication bias

Evaluation of publication bias suggested presence of bias for female gender ($t=2.683$, one tailed, $p=0.009$, online supplementary figure 1A). Simulation by the ‘trim and fill’ method was employed to determine missing studies based on the random effects model, and the imputed point estimate was changed to 2.45 (95% CI 1.84 to 3.26). Publication bias was also found for age ($t=5.720$, one tailed, $p<0.001$, online supplementary figure 1B), and the adjusted point estimate was modified to 1.24 (95% CI –1.16 to 3.68) with simulation via the ‘trim and fill’ method. As shown in online supplementary figure 1C, there was no significant evidence of publication bias in regard to HTN via Egger’s test ($t=0.600$, one tailed, $p=0.280$).

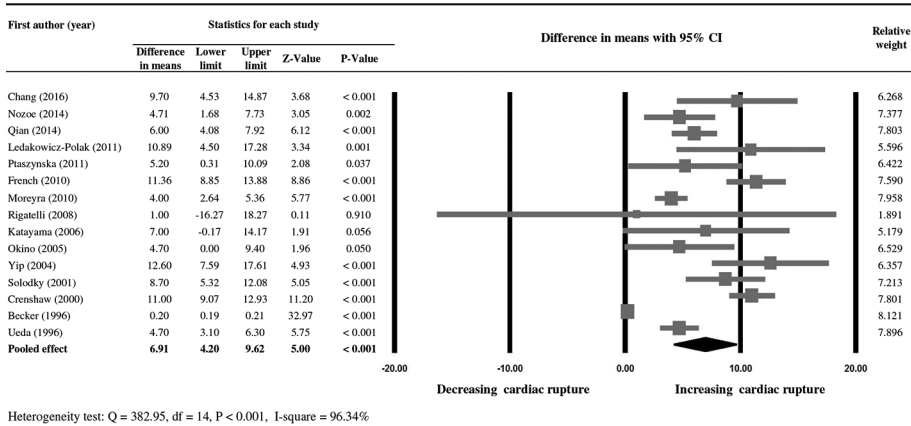
Additional specific subgroup analysis

Risk factors associated with the occurrence of CR within specific subgroups are summarized in table 3. In the VSR subgroup, female gender (pooled OR=4.49, $p<0.001$), older age (pooled mean difference=9.12, $p<0.001$), and LAD involvement (pooled OR=2.93, $p=0.001$) were significantly associated with increased risk of VSR. In patients with STEMI,

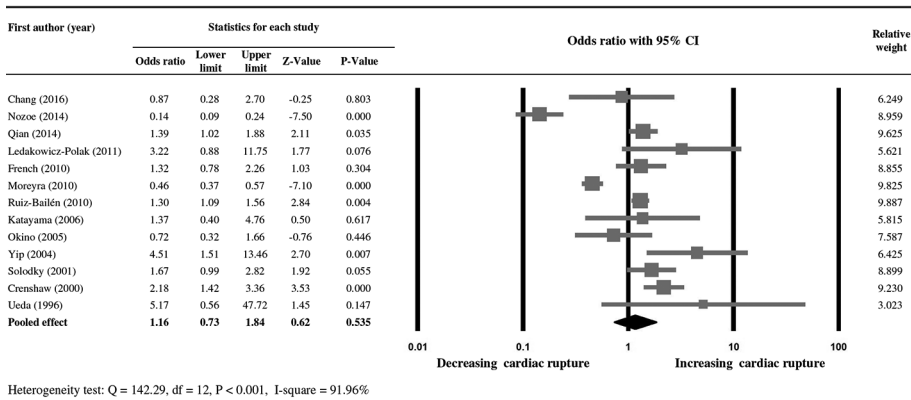
A. Female gender



B. Age



C. Hypertension



D. History of myocardial infarction

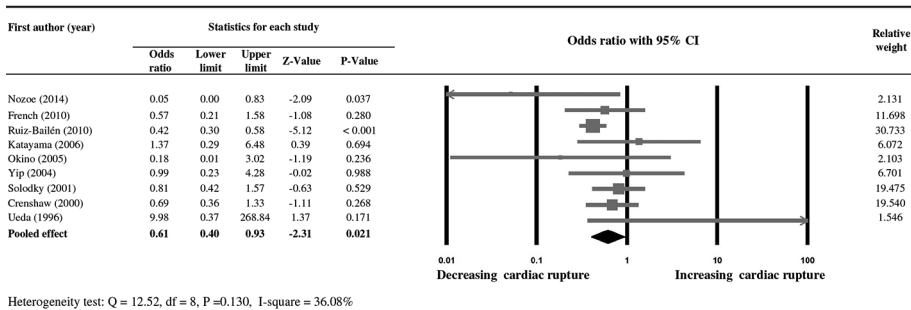


Figure 2 Meta-analysis for outcomes. (A) Female gender; (B) age; (C) hypertension; and (D) history of myocardial infarction.

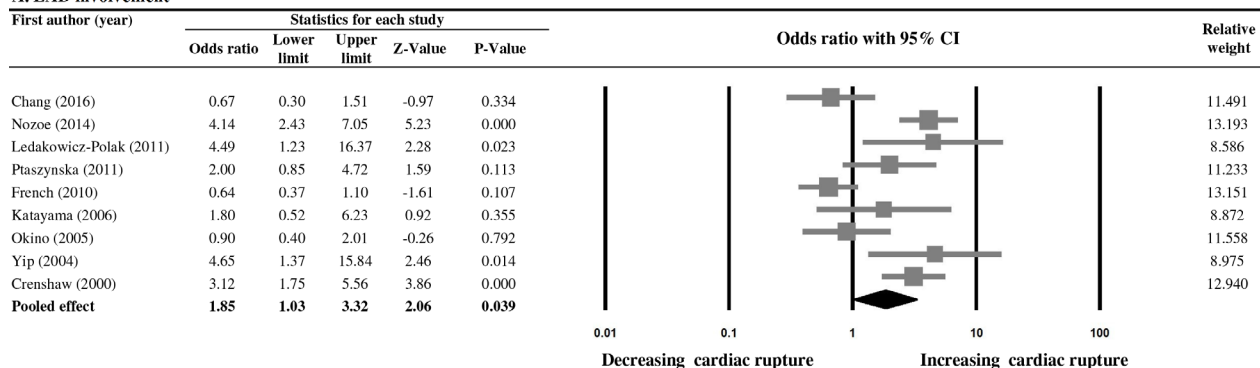
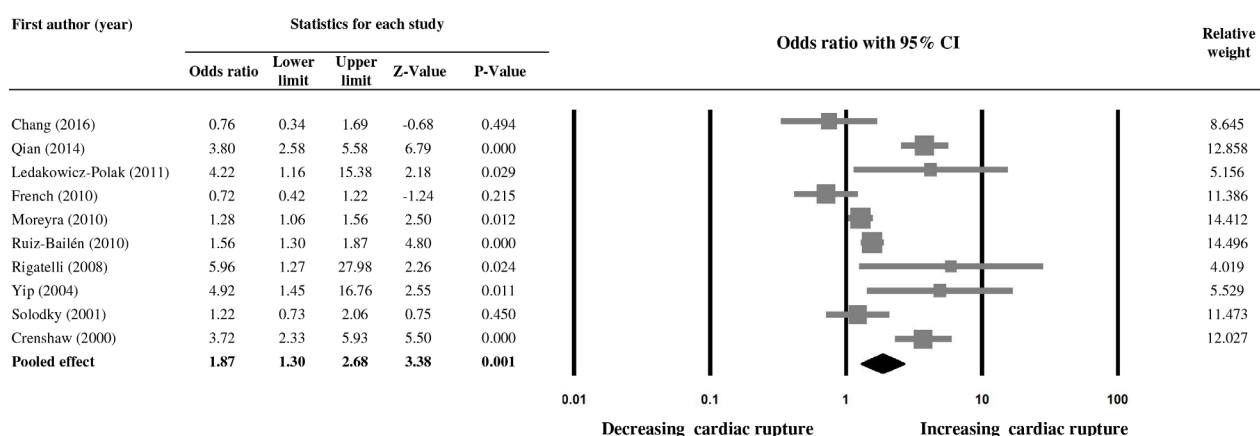
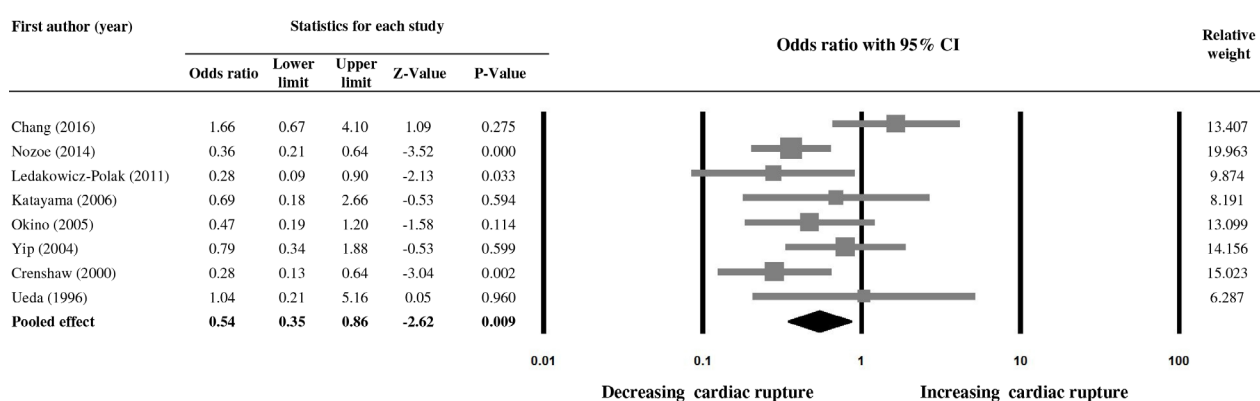
A. LAD involvement**B. ant. Wall Infarction****C. Multivessel involvement**

Figure 3 Meta-analysis for outcomes. (A) LAD involvement; (B) anterior wall infarction; and (C) multivessel involvement. ant, anterior; LAD, left anterior descending coronary artery.

only female gender (pooled OR=2.71, $p < 0.001$) and older age (pooled mean difference=7.51, $p < 0.001$) were significantly associated with increased risk of CR. Furthermore, female gender (pooled OR=3.16, $p < 0.001$) and older age

(pooled mean difference=7.30, $p < 0.001$) were significant independent risk factors for increased risk of CR in studies published after 2000. Patients with multivessel disease had decreased risk of CR in the VSR subgroup (pooled OR=0.36,

Table 2 Meta-analysis of selected studies

Risk factors	Studies (n)	Q statistics	I ² (%)	Pooled effect size with 95% CI	P values
DM	12	25.65	57.12	1.01 (0.85 to 1.35)	0.565
Dyslipidemia	7	19.15	68.66	0.74 (0.49 to 1.12)	0.159
Previous PCI	2	2.74	63.44	0.21 (0.02 to 2.30)	0.199
Previous CABG	3	0.50	0.00	0.96 (0.41 to 2.25)	0.929
History of angina	2	0.23	0.00	0.71 (0.44 to 1.17)	0.179
Smoking	9	11.87	32.63	0.40 (0.32 to 0.50)	<0.001
Killip IV	7	20.08	70.11	10.14 (9.14 to 14.39)	<0.001
Statin use	2	3.76	73.42	0.22 (0.02 to 3.23)	0.269
β-blocker use	3	23.41	91.46	0.40 (0.18 to 0.87)	0.021
ACEI/ARB use	3	4.06	50.74	0.62 (0.47 to 0.82)	0.001
LCX involved	8	13.11	46.61	0.70 (0.36 to 1.34)	0.275
RCA involved	8	10.00	29.99	0.66 (0.47 to 0.93)	0.018
LM involved	6	2.79	0.00	5.51 (2.44 to 12.46)	<0.001
Inferior/lateral wall infarction	3	6.05	66.96	0.91 (0.69 to 1.20)	0.500
Primary PCI	5	25.35	84.22	0.33 (0.17 to 0.62)	0.001
Thrombolysis	6	19.86	74.82	2.03 (1.30 to 3.17)	0.002
Dual antiplatelet treatment	2	2.4	58.39	0.49 (0.21 to 1.15)	0.102

ACEI, ACE inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; DM, diabetes mellitus; LCX, left circumflex; LM, left main; PCI, percutaneous coronary intervention; RCA, right coronary artery.

$p=0.001$) as well as in studies published after 2000 (pooled OR=0.35, $p<0.001$).

Quality assessment

The quality of the included studies was evaluated using ACROBAT-NRSI, and the results are shown in online supplementary figure 2A,B. Most of the 16 included

studies had low risk of bias in terms of confounding, selection of subjects, measurement of interventions, missing data, measurement of outcomes, and selection of the reported result. Ledakowicz-Polak *et al*,²⁰ French *et al*,²¹ and Ueda *et al*¹⁹ had high risk of bias due to confounding. Overall, the quality of the included studies is good.

Table 3 Additional subgroup analysis

Risk factors	Studies (n)	Q statistics	I ² (%)	Pooled effect size with 95% CI	P values
VSR					
Gender	6	35	85.72	4.49 (2.26 to 8.91)	<0.001
Age	5	41.55	90.37	9.12 (4.78 to 13.46)	<0.001
HTN	6	75.93	93.42	1.09 (0.38 to 3.15)	0.877
History of MI	4	1.25	0.00	0.67 (0.38 to 1.19)	0.175
LAD involvement	5	7.05	43.28	2.93 (1.59 to 5.39)	0.001
Anterior wall infarction	5	26.19	84.73	2.13 (1.00 to 4.54)	0.049
Multivessel disease	4	3.067	67.39	0.36 (0.19 to 0.68)	0.001
With ST elevation					
Gender	6	25.32	80.25	2.71 (1.73 to 4.25)	<0.001
Age	6	30.1	83.39	7.51 (4.65 to 10.37)	<0.001
HTN	5	45.17	91.14	1.09 (0.54 to 2.19)	0.814
History of MI	1	NA		NA	
LAD involvement	4	11.18	73.17	1.24 (0.56 to 2.75)	0.605
Anterior wall infarction	5	37.43	89.31	1.54 (0.80 to 2.97)	0.202
Multivessel disease	2	5.54	81.95	0.71 (0.12 to 4.04)	0.698
Study after year 2000					
Gender	6	10.46	52.22	3.16 (2.17 to 4.59)	<0.001
Age	6	17.05	70.66	7.30 (4.45 to 10.15)	<0.001
HTN	4	63.88	95.30	0.90 (0.27 to 3.07)	0.871
History of MI	2	2.53	60.47	0.25 (0.03 to 2.33)	0.222
LAD involvement	4	25.4	88.19	2.11 (0.74 to 6.06)	0.165
Anterior wall infarction	4	0.306	0.00	2.62 (0.86 to 7.95)	0.09
Multivessel disease	2	0.15	0.00	0.35 (0.21 to 0.57)	<0.001

HTN, hypertension; LAD, left anterior descending coronary artery; MI, myocardial infarction; NA, not available; VSR, ventricular septal rupture.

DISCUSSION

This study was a meta-analysis to determine possible risk factors for CR in patients with AMI. The results revealed that patients with AMI with the following features are at increased risk of CR: female gender, older age, Killip class IV MI, anterior wall infarction, single-vessel disease, LAD involvement, LM involvement, and treatment with thrombolysis. In contrast, reduced risk of CR in patients with AMI was found with history of MI, smoking, use of β -blocker or ACEI/ARB, RCA involvement, and treatment with primary PCI. These findings may aid in the identification of patients with AMI at increased risk of CR in future clinical practice.

A previous meta-analysis included patients with AMI who were studied at necropsy between 1968 and 1988, and the results showed that among the rupture cases, the frequency of left FWR and VSR was 67% and 27%, respectively. When rupture and non-rupture cases were compared, no significant difference was observed in age, proportion of patients with history of systemic HTN, or mean heart weight in both male and female patients. However, significant differences were found between rupture and non-rupture cases in the proportion of men (55% vs 70%) and women (45% vs 30%), proportion of patients with diabetes mellitus (13% vs 27%), and the presence of left ventricular scar (13% vs 42%). Although no significant difference was observed in age overall, age in women (73 vs 69 years) was significantly different between rupture and non-rupture groups.²³ Results of the current analysis suggest that older age is an independent risk factor for CR. It should be noted, however, that in clinical practice, the majority of female patients with MI are of advanced age. Therefore, the influence of gender may be in fact due, at least in part, to advanced age.

Certain demographic and clinical characteristics of patients with AMI are among the factors that have been associated with increased risk of CR. Most of the included studies concluded that there was increased risk of CR in female and older patients. Indeed, the predisposition of female patients to CR may be related to a more susceptible collagen framework due to differences in the myocardial collagen matrix,²⁴ as well as differences in inflammatory response²⁵ and genetic differences.²⁶ The included studies had conflicting results in regard to HTN. HTN was associated with decreased risk of VSR in concentric cardiac hypertrophy in some studies, yet other studies suggested that HTN has an important role in the pathogenesis of VSR.^{27–29} Diabetes mellitus, which affects collateral arterial circulation, was not associated with a significant increase in risk for CR in our study.

Treatment with ACEI/ARB and β -blocker agents may have cardioprotective effects that help prevent CR.^{30–31} Inhibition of the renin-angiotensin system has been shown to block the release of splenic monocytes and neutrophils into the circulation, consequently attenuating the infiltration of these cells in the infarcted myocardium.^{32–33} Treatment with ACEI and β -blockers is thought to prevent neurohormonal activation and destructive myocardial remodelling,³⁴ and β -blocker treatment is believed to lessen inflammation when serum C-reactive protein level is reduced.³⁵ Interestingly, patients with history of smoking had reduced risk of CR, which may be related to the effect of smoking on coronary collateral circulation.³⁶ Moreover, patients without history of MI had an increased risk of CR, possibly due to lack of myocardial preconditioning and prevalence of collateral arteries.³⁷ A mouse model study has

shown that pre-existing cardiac hypertrophy and interstitial fibrosis may allow the ventricular wall to be more resistant to damage mediated by inflammation.³²

LAD involvement, LM involvement, and anterior wall infarction were MI characteristics associated with increased risk of CR. In contrast, patients with multivessel involvement had decreased risk of CR, as did patients with Killip class IV MI. A mouse MI model has demonstrated that a critical level of infarct size (>30%) was necessary for CR and that the reduction of muscle tensile strength also correlated with infarct size.³⁸ In terms of treatment for MI, our study showed that patients who had undergone primary PCI had decreased risk for CR, while patients who had received thrombolytic therapy had higher risk for CR. The results correspond to the observation that the incidence of CR has dramatically decreased in the PCI era.^{22–39} The association between thrombolysis and increased risk of CR may be due to thrombolysis-induced stimulation of plasmin, which increases collagenolysis and inhibits collagen synthesis, triggering a cascade that could cause intramural hemorrhage leading to CR.¹⁷ The timing of thrombolytic therapy for AMI has been shown to be associated with CR risk, with more prolonged time to treatment after MI associated with increasing risk (7 hours, OR=0.4; 11 hours, OR=0.93; 17 hours, OR=3.21).⁴⁰ Furthermore, the median time to VSR formation post-MI was significantly shorter in patients receiving thrombolysis treatment than in those without thrombolysis treatment, and compared with late thrombolysis treatment, early thrombolysis treatment was associated with shorter median time to post-MI VSR formation.⁴¹

Results of subgroup analyses showed that in the subgroup of patients with VSR, female gender, older age, and LAD involvement remained risk factors for CR. In the subgroup of patients with STEMI, the risk factors were female gender and older age. The use of PCI has been routine in clinical practice since the year 2000, and this marked shift in standard therapy should be considered when pooling data collected between 1980 and 2013. Therefore, we conducted a subgroup analysis of the studies published after 2000, which showed that there was no apparent difference in risk factors for CR between overall studies and studies after 2000. Although the number of studies included in each subgroup analysis was limited, there seems to be no significant difference between the overall results and results of the VSR subgroup. The impact of LAD involvement, anterior wall infarction and multivessel disease in patients with STEMI, however, warrants further research.

There are some limitations in this study. First, all of the included studies were retrospective in nature. Comparative cohort studies for the evaluation of CR in patients with AMI are warranted. Second, the occurrence of CR is likely to be underestimated due to patients with sudden death without definite cause or autopsy. Third, the number of included studies for some factors is small, such as those reporting on use of statin, β -blocker, ACEI/ARB, and dual antiplatelet treatment. Finally, heterogeneity existed among the included studies, which may be a result of large variations in patient numbers, procedures, and pharmaceutical treatments. Future studies to investigate differences in risk factors among CR subtypes, to evaluate the impact of timing of reperfusion on the risk of CR, as well as to identify accurate biomarkers for prediction of CR are needed.

CONCLUSIONS

The risk factors for CR in patients with AMI included female gender, older age, recent MI, non-smoking status, LAD involvement, LM involvement, anterior wall infarction, and single-vessel disease. Treatment with primary PCI could help reduce the risk of CR, while thrombolysis could increase the risk.

Contributors SN contributed to study design. WH contributed to literature research and manuscript preparation. SL contributed to literature research. JF and LZ contributed to data acquisition and analysis.

Funding This study was supported by the Beijing Natural Science Foundation (7141003), the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ZYLX201710) and the Cardiovascular Disease Big Data Platform Development and Applied Research Project (2015AA020102).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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