Systematic Review

Systematic review and meta-analysis of the mechanical complications of ischemic heart disease: papillary muscle rupture, left ventricle rupture and post-infarct ventricular septal defect

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Background: Improvements in revascularisation, including pharmacological, catheter-based and surgical, have resulted in improved outcomes for patients with acute myocardial infarction (AMI), leading to decreased frequency of mechanical complications. Improvements in both techniques and technology have permitted select patients to be managed with a purely percutaneous, transcatheter strategy. Through systematic review, this study aims to synthesise the collective experience of percutaneous treatment of the mechanical complications of ischaemic heart disease.

Methods: The search strategy queried the electronic databases PubMed, Embase and the Cochrane Central Register of Controlled Trials, from 1 January 2000 to 31 December 2020. Studies highlighting the outcomes of patients receiving percutaneous treatment of post-myocardial infarction papillary muscle rupture (PMR), ventricular septal defect (VSD), left ventricular free wall rupture (FWR) and pseudoaneurysm (PA) were included. A qualitative review of studies was conducted for PMR, FWR and PA. A quantitative analysis was conducted for VSD.

Results: Fifteen studies were included in the qualitative synthesis of the percutaneous management of PMR, 4 were included in the qualitative analysis of the percutaneous management of left ventricular FWR, 7 studies defined the outcomes of the percutaneous management of PA and 25 were included in the quantitative meta-analysis of the primary percutaneous management of post-MI VSD. For VSD, there were 43 failed procedures in 314 patients. The proportion of failed procedures was 15.9% and there were 174 deaths in 428 patients. 37.5% of patients experienced early mortality.

Conclusions: Although surgical techniques remain the gold standard, we have shown that percutaneous management may be a viable option in certain cases.

Keywords: Mechanical complication; ventricular septal defect; papillary muscle rupture; ventricular pseudoaneurysm; ischaemic heart disease

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Introduction

Improvements in revascularisation, including pharmacological, catheter-based and surgical, have resulted in improved outcomes for patients with acute myocardial infarction (AMI), leading to decreased frequency of mechanical complications (1,2). Large infarcts, delayed hospital presentation and a lack of tissue perfusion due to poor coronary flow post-intervention, are risk factors for mechanical complications including; acute mitral regurgitation (MR) secondary to papillary muscle rupture (PMR), ventricular septal defect (VSD), pseudoaneurysm and free wall rupture (FWR) (3). Although the incidence of mechanical complications following AMI has declined at <1%, the mortality rates have not decreased (4). Patients who go on to develop mechanical complications tend to be older, female, have a history of cardiac failure, chronic kidney disease and are often presenting with their first AMI (3).

Papillary muscle rupture presents 3–5 days following transmural inferior or lateral infarct, with resultant posteromedial PMR, typically in acute pulmonary oedema and cardiogenic shock. The incidence of acute severe MR from PMR is around 0.05–0.26%, with a reported mortality rate of 10–40% (3). Ventricular septal defects carry a high mortality of 30–40% acutely and up to 80% at 30 days, typically presenting 3–5 days after transmural infarct, with symptoms ranging from isolated murmur to circulatory collapse with cardiogenic shock (3). Free wall rupture remains the most reported mechanical complication, however, the true incidence is unknown as it usually presents as an out-of-hospital sudden cardiac death within 7 days, following a transmural infarct (4). Left ventricular pseudoaneurysms typically present weeks to years following infarct, when cardiac rupture is contained by pericardial adhesions and may be asymptomatic or present with chronic heart failure, chest pain or dyspnoea (4). Given their high risk for progression and rupture, consideration of urgent surgical repair is prudent with an estimated mortality of <10% (3).

All mechanical complications of ischaemic heart disease (IHD) conventionally require surgical intervention. However, with improvements in techniques and technology, select patients can be managed with a purely percutaneous, transcatheter strategy. Most mechanical complications are high-acuity and time-sensitive surgical emergencies, requiring prompt discussion with cardiac surgery, cardiac intensivists and cardiologists to diagnose and manage. Given the vast array of management options with advances in transcatheter technology, multidisciplinary discussions involving the patient and family's preference for care should be undertaken in this population with a high mortality risk, regardless of treatment strategy (4).

Aim

Through systematic review, this study aims to synthesise the collective experience of percutaneous treatment of the mechanical complications of ischaemic heart disease.

Methods

Search strategy

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and guidelines. The search strategy queried the electronic databases PubMed, Embase and the Cochrane Central Register of Controlled Trials from 1 January 2000 to 31 December 2020. The search terms were: ventricular free-wall rupture OR ventricular pseudoaneurysm AND percutaneous treatment; ventricular septal rupture OR ventricular septal defect AND percutaneous treatment; papillary muscle rupture AND percutaneous treatment. The reference lists of previous systematic reviews and of included studies were assessed to ensure no additional publications were missed.

Inclusion criteria

A qualitative assessment of the percutaneous treatment of ventricular FWR and PMR was undertaken, given the limited experience reported in the literature. The inclusion criteria for the qualitative assessment were all-English language papers (including case reports), with sufficient outcome data reported. Conference abstracts, review articles, editorials and letters were excluded. Papers for inclusion were independently identified and verified (MG, DR, LM and FT).

A quantitative assessment of the primary percutaneous treatment of post-myocardial infarction (PMI) VSD was undertaken. Eligibility for inclusion in this quantitative component were all studies that assessed outcomes of patients undergoing percutaneous treatment of post-infarct VSD as the first treatment. To ensure sufficient centre experience, papers were only included if more than five

cases were reported. Only English language papers were analyzed. If centres reported outcomes of overlapping patient series, the most complete, contemporary series was analyzed. Conference abstracts, case reports, editorials, reviews, letters and expert opinion pieces were excluded. Studies detailing the outcomes of the percutaneous treatment of failed previous surgical treatment in post-MI VSD were excluded, as were studies detailing congenital VSD repair. Article identification and inclusion were performed independently by three authors (CDF, PM and MM) and, discussed until consensus was reached.

Data extraction

Data was extracted from the reviewed text, tables and figures. Data was extracted independently by the authors and, any discrepancies were reviewed and discussed until consensus was reached. For the qualitative synthesis, recorded data included: demographic data, acuity of presentation, procedural success, early and follow-up mortality. For the quantitative synthesis, recorded parameters were: number of cases in series, demographic data, follow-up duration, acuity treatment, presence of cardiogenic shock at time of treatment, procedural success, presence and significance of residual trans-septal shunt at discharge from hospital, requirement for subsequent procedures (percutaneous or surgical), timing of treatment and early mortality.

Statistical methods

Meta-analysis of post-operative observations was performed using R (R version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). For publications reporting continuous variables, central tendency with median and range values, the mean and standard deviation were estimated using calculations described by Wan *et al.* (5). Given the range of publication dates and operation techniques, significant between-study heterogeneity was anticipated thus, a random effects model was used in all cases. Heterogeneity was assessed using the I^2 test statistic and determination of prediction intervals. Low heterogeneity was denoted by $I^2<50\%$, moderate heterogeneity by $50\%\leq I^2<75\%$ and high heterogeneity by $I^2\geq75\%$. For continuous variables, the restricted maximum likelihood estimator was used to calculate heterogeneity variance. Binary data was logit transformed and assessment of heterogeneity was conducted using the DerSimonian-Laird estimator. A Knapp-Hartung adjustment was used to calculate the confidence interval of the pooled outcome effect.

Quality assessment

For the quantitative analysis, study quality was assessed using the risk of bias in non-randomised studies of interventions (ROBINS-i) tool (6). Study quality was independently assessed by two investigators (CDF and PM) until consensus was reached.

Assessment of bias and individual study influence

Publication bias was assessed through visual inspection and statistical analysis of funnel plots. Statistical analysis of funnel plot asymmetry was conducted using Egger's regression test. Regression analysis of plot asymmetry was only conducted in instances where more than 10 studies were analysed. In the event of significant publication bias, Duval and Tweedie's trim-and-fill method was applied to correct for publication and small study bias. Leave-one-out sensitivity analysis was conducted to determine the significance of study influence.

Results

The search strategy revealed 3,051 unique articles that underwent title and abstract review, which led to 2,905 studies being excluded. Of the remaining 146 studies, 15 studies were included in the qualitative synthesis of the percutaneous management of PMR (7-21), 4 were included in the qualitative analysis of the percutaneous management of LV FWR (22-25), 7 studies defined the outcomes of the percutaneous management of LV pseudoaneurysm (15,26-41) and 25 were included in the quantitative meta-analysis of the primary percutaneous management of post-MI VSD (42-66) (*Table 1*) (Figure S1).

Qualitative synthesis of the percutaneous treatment of mechanical complication of ischaemic heart disease

Papillary muscle rupture (PMR)

Fifteen studies focused on novel treatments of PMR, including 42 patients with an age range of 51–85 (7-21). 24 patients presented in cardiogenic shock (8-15,17,19-21), 22 with pulmonary oedema (8-12,14-21) and 23 required mechanical circulatory support (8-13,15-21) (*Table 2*). On

Table 1 Study characteristics for meta-analysis of outcomes of the percutaneous treatment of post-MI VSD

Study	Location	Study design	Study focus	Patients (n)	Males (n)	Age ± SD	Study duration	Follow-up years (± SD)
Maltais, 2009	Quebec, Canada	Retrospective single centre	Percutaneous Advances of PMI-VSD Closure	12	–	71.3±7.7	12	–
Trivedi, 2015	Marseille, France	Retrospective multicentre	Sequential Management of PMI-VSDs	8	–	75.5±7.0	6	–
Bialkowski, 2007	Zabrze, Poland	Retrospective single centre	Transcatheter Closure of PMI-VSDs Using Amplatzer Devices	17	13	66.3±8.1	6	–
Aggarwal, 2018	Kerala, India	Retrospective single centre	ASD Occluder Usage in PMI-VSR	21	15	66.4±5.9	14	–
Ahmed, 2007	Auckland, New Zealand	Retrospective single centre	Percutaneous Closure of PMI-VSD	4	2	73±4.7	3	1.95±1.2
Assenza, 2013	Boston, USA	Retrospective single centre	Transcatheter closure of PMI-VSR	12	8	68±6	20	–
Martinez, 2007	Minnesota, USA	Retrospective single centre	Transcatheter Closure of Ischemic and Post-Traumatic VSRs	4	2	73±16.5	–	4.5
Demkow, 2005	Warsaw, Poland	Retrospective single centre	Primary Transcatheter Closure of PMI-VSDs with Amplatzer Septal Occluder	11	9	67.8±8.9	6	3.07±1.6
Egbe, 2015	Minnesota, USA	Retrospective single centre	Transcatheter Closure of PMI, Iatrogenic and Postoperative VSDs	18	7	69±11	14	7.3±7
Nie, 2017	Taipei, Taiwan	Retrospective multicentre	Transcatheter Device Closure of PMI-VSD	7	5	74.4±7.8	3	–
Premchand, 2017	Hyderabad, India	Retrospective single centre	Percutaneous Closure of PMI-VSR	7	2	58.3±9.8	10	–
Goldsweig, 2018	Connecticut, USA	Retrospective multicentre	VSR Complicating AMI	84	–	–	9	–
Hamilton, 2017	Bristol, UK	Retrospective single centre	The In Vivo Morphology of PMI-VSD and Implications for Closure	16	–	–	10	–
Heiberh, 2014	Aarhus, Denmark	Retrospective single centre	Long-Term Outcome after Transcatheter Closure of PMI-VSR	9	4	75.1±8.4	13	4.6±4.4
Landzberg, 1998	Boston, USA	Prospective single centre	Transcatheter Management of PMI-VSRs	7	–	–	8	
Sabiniewicz, 2017	Warsaw, Poland	Retrospective multicentre	Percutaneous Closure of PMI-VSDs	20	11	70.2±9.5	13	1.32±2.6
Sathananthan, 2013	Auckland, New Zealand	Retrospective single centre	Evolution in PMI-VSD Management	7	–	–	20	–
Rao, 2015	Hyderabad, India	Prospective single centre	Transcatheter closure of PMI-VSR	6	5	60±3.7	3	
Szkutnik, 2003	Zabrze, Poland	Prospective single centre	PMI-VSD Closure with Amplatzer Occluders	6	5	59.7±8.1	–	9.1±5.8
Tai, 2018	Hengyang, China	Retrospective multicentre	Management and Outcome of VSR Complicating AMI	20	–	–	10	

Table 1 (*continued*)

Table 1 (*continued*)

Study	Location	Study design	Study focus	Patients (n)	Males (n)	Age ± SD	Study duration	Follow-up years (± SD)
Tang, 2015	Hunan, China	Retrospective single centre	Non-Surgical Repair of VSR After AMI	11	4	65.25±7.9	7	2.55±1.7
Thiele, 2009	Leipzig, Germany	Prospective single centre	Immediate Primary Transcatheter Closure of PMI-VSD	29	13	69±8.9	5	3.84
Xu, 2014	Shanghai, China	Retrospective multicentre	Percutaneous Closure of PMI-VSDs	42	4	–	4	2.25±1.1
Zhang, 2017	Harbin, China	Retrospective multicentre	Percutaneous Transcatheter Closure of PMI-VSDs: Outcomes and Follow-Up	15	6	63.1±7.3	12	7.6±0.9
Zhu, 2013	Shenyang, China	Retrospective multicentre	Outcomes of Transcatheter Closure of VSD in Combination with PCI in Patients with VSD Complicating AMI	35	18	63.5±5.5	10	4.42

MI, myocardial infarction; VSD, ventricular septal defect; PMI, post-myocardial infarction; ASD, atrial septal defect; VSR, ventricular septal rupture; PCI, percutaneous coronary intervention.

Table 2 Baseline characteristics of patients receiving percutaneous treatment of papillary muscle rupture post-acute MI

Author	Year	Patients (n)	Age [range]	Cardiogenic shock [%]	Pulmonary Oedema [%]	MCS [%]	STEMI [%]	NSTEMI [%]	PTCA [%]	PMR [%]	Not PMR [%]
Bilge	2013	1	60	1 [100]	1 [100]	1[a] [100]	1 [100]	0	1 [100]	1 [100]	0
Adamo	2014	5	72 [62–78]	4 [80]	4 [80]	4[a] [80]	5 [100]	0	5 [100]	0	5 [100]
Bilge	2014	1	73	–	–	–	–	–	1 [100]	1 [100]	0
Horstkotte	2014	1	75	1 [100]	1 [100]	1[a] [100]	1 [100]	0	1 [100]	1 [100]	0
Wolff	2014	1	68	1 [100]	1 [100]	1[a] [100]	1 [100]	0	1 [100]	1 [100]	0
Bahlmann	2015	1	77	1 [100]	1 [100]	1[a] [100]	0	1 [100]	–	1 [100]	0
Estevez-Loureiro	2015	5	68 [51–76]	3 [60]	–	3[a] [60]	3 [60]	2 [40]	–	0	5 [100]
Rodriguez	2015	1	76	1 [100]	1 [100]	–	1 [100]	0	1 [100]	0	1 [100]
Alkhouli	2017	1	77	1 [100]	1 [100]	1[b]	0	1 [100]	1 [100]	0	1 [100]
Tarsia	2016	1	65	–	1 [100]	1[a] [100]	1 [100]	0	1 [100]	0	1 [100]
Valle	2017	1	84	1 [100]	1 [100]	–	0	1 [100]	1 [100]	1 [100]	0
Yasin	2018	1	68	0	1 [100]	1[c] [100]	–	–	1 [100]	1 [100]	0
Komatsu	2019	1	55	1 [100]	1 [100]	1[a] [100]	1 [100]	0	1 [100]	1 [100]	0
Papadopoulos	2019	1	85	1 [100]	1 [100]	1[a] [100]	1 [100]	0	1 [100]	1 [100]	0
Haberman	2019	20	68 [53–85]	8 [40]	7 [35]	7[a] [35]	12 [60]	8 [40]	17 [85]	0	20 [100]
Total[#]	–	42	72 [51–85]	24 [60]	22 [61]	23 [59]	27 [69]	13 [38]	33 [92]	9 [21]	33 [79]

[#], percentage calculation for summary totals only include patients in studies directly reporting outcome of interest. [a], intra-aortic balloon pump; [b], Impella device; [c], ECMO, extracorporeal membrane oxygenation; MCS, mechanical circulatory support; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PTCA, percutaneous transcatheter coronary angioplasty; PMR, papillary muscle rupture; MI, myocardial infarction.

Table 3 Procedural outcomes following percutaneous repair of papillary muscle rupture following acute-MI

Author	Year	Patients (n)	ICU (days) [range]	Discharge (day) [range]	Complication	30 day-Mortality [%]	NYHA	Grade MR residual [n]	Mortality at follow up [%]	Cause of death
Bilge	2013	1	–	9	Stroke	0	–	–	0	–
Adamo	2014	5	8 [7–10]	27 [13–60]	-	0	II	1+ [1], 2+ [1], 3+ [1]	2	Septic shock heart failure
Bilge	2014	1	–	–	–	–	–	–	–	–
Horstkotte	2014	1	7	12	0	0	–	1+ [1]	0	–
Wolff	2014	1	–	14	–	0	II	1+ [1]	0	–
Bahlmann	2015	1	8	16	0	–	–	–	–	–
Estevez-Loureiro	2015	5	–	–	–	1 [20]	II	1+ [2], 2+ [3]	1	MOFs
Rodriguez	2015	1	–	–	–	–	–	–	–	–
Alkhouli	2017	1	6	–	–	0	I	–	0	–
Tarsia	2016	1	7	–	0	0	I	0	0	–
Valle	2017	1	4	–	–	0	II	1+ [1]	0	–
Yasin	2018	1	–	–	BAV II	0	–	1+ [1]	0	–
Komatsu	2019	1			0	0			0	–
Papadopoulos	2019	1	–	19	0	0	II	2+ [1]	0	–
Haberman	2019	20	–	–	–	0	NA	1+ [12], 2+ [7]	1	Sudden death
Total[#]	–	42	7 [4–10]	15 [9–60]	–	1 [3]		–	4 [10]	

[#], percentage calculation for summary totals only include patients in studies directly reporting outcome of interest. MI, myocardial infarction; ICU, Intensive care unit; NYHA, New York Heart Association heart failure grade; MOF, multi-organ failure.

presentation, 33 patients underwent percutaneous coronary intervention (7-11,14-21), with 27 diagnosed with a STEMI (8-11,13,14,16,19-21) and 13 NSTEMI (12,13,15,17,21). All patients underwent percutaneous edge-to-edge repair of mitral valve using the MitraClip system, with successful deployment. Residual moderate-severe MR was reported in 13 patients (8,13,20,21). Only two manuscripts reported complications of stroke and heart block requiring permanent pacemaker insertion (9,18). There was one reported 30-day mortality (13) and four deaths at time of follow-up (8,13,21) (*Table 3*).

Left ventricular free wall rupture (FWR)

Four manuscripts reviewed the management of FWR, including 26 patients with an age range of 51–87 years old (22-25). All patients presented with cardiac tamponade, with 16 patients in concurrent cardiogenic shock, of which, eight required mechanical circulatory support (22-25). Of these, three patients suffered a STEMI (22,23,25) and 19 underwent percutaneous coronary intervention (22,24,25) (*Table 4*). Due to high-risk conditions, all FWR patients were treated with fibrin-glue injection. Complications occurred in two patients, with one requiring surgical repair and another suffering from acute respiratory distress syndrome (ARDS) and sepsis (22,24). However, 30-day mortality was high, with 16 early deaths attributed to septic shock, acute rupture, re-rupture or non-cardiac causation, and 17 at time of follow-up (22,24) (*Table 5*).

Ventricular pseudoaneurysm

Seventeen studies described techniques for ventricular pseudoaneurysm management, including 19 patients with

Table 4 Baseline patient characteristics for patients receiving percutaneous treatment of left ventricular free wall rupture post acute MI

Author	Year	Patients (n)	Age [range]	Cardiogenic shock [%]	Tamponade [%]	MCS [%]	STEMI [%]	NSTEMI [%]	PTCA [%]
Murata	2000	2	69 [56–81]	2 [100]	2 [100]	1 [50]	1 [50]	0	2 [100]
Joho	2002	1	82	0	1 [100]	0	1 [100]	0	0
Terashima	2008	22	74 [51–87]	13 [59]	22 [100]	6	–	–	16 [72.7]
Suzuki	2019	1	65	1 [100]	1 [100]	1 [100]	1 [100]	–	1 [100]

MI, myocardial infarction; MCS, mechanical circulatory support; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PTCA, percutaneous transcatheter coronary angioplasty.

Table 5 Procedural outcomes and complications following percutaneous repair of LV free wall rupture

Author	Year	Patients (n)	Discharge [day]	Complication	30-day mortality [%]	NYHA	Residual effusion/ aneurysm	Mortality at follow up (%)	Cause of death
Murata	2000	2	20 [10–30]	Sepsis, ARDS	1 [50]	–	0	50	Septic shock
Joho	2002	1	14	–	0	–	0	0	
Terashima	2008	22	–	Required surgical repair (1 patient)	15 [68]	1	0	73	Acute rupture (13 patients), re-rupture (2 patients), non-cardiac (1 patient)
Suzuki	2019	1	62	–	0	–	0	0	

LV, left ventricular; NYHA, New York Heart Association, heart failure grade.

an age range of 47–85 (15,26-41). Two patients presented with cardiogenic shock (15,39), eight with dyspnoea (15,26,28,31,33,34,38,40) and one required mechanical circulatory support (39). Six patients underwent subsequent percutaneous coronary intervention (33,34,36,37,39,41) and 12 were diagnosed with a STEMI (15,26,27,31-38,41) (*Table 6*). Due to significant comorbidities, including previous cardiac surgery, COPD, diabetes and previous CVA, all patients underwent percutaneous repair with a closure device. A residual pseudoaneurysm was reported in one patient following attempted closure (34). There were no early deaths and only one mortality at follow-up, due to recurrent pulmonary embolus (27) (*Table 7*).

Meta-analysis of post-infarct VSD

Study quality and risk of bias assessment

The overall risk of bias was moderate to severe for all 25 included studies (*Figure 1*). There were 7 studies (43,47,51,53,58,59,63) graded with an overall severe risk and 18 studies (42,44-46,48-50,52,54-57,60-62,64-66) graded at overall moderate risk, of bias. The most significant risks of bias were identified in confounding, selection bias and selection of reported outcomes.

Demographic data

The total number of patients in the analysis was 428. Average age was reliably reported in 19 studies (42-47,50, 52-56,58,59,61-63,65,66) with a pooled mean age of 67.6 years-old [95% confidence interval (CI): 65.4–69.9, I^2=80.3%]. Eighteen studies (42-47,50,53-56,58-62,65,66) provided data regarding patient gender. In these studies, 48.5% of patients (133 of 274 patients) were male. Duration of data collection was clearly reported in 25 studies (42-52, 54-58,60-66), which collected data over a mean duration of 9.5±4.9 years. The median number of annual cases in the studies reporting data was 1.5 [inter-quartile range (IQR) 1.0] cases per year (*Table 1*).

Mortality outcomes

All 25 studies reported outcomes on mortality. There were 174 deaths in 428 patients. The proportion of patients

Table 6 Baseline patient characteristics for patients receiving percutaneous treatment of left ventricular pseudoaneurysm post-acute MI

Author	Year	Patients (n)	Age [range]	Cardiogenic shock [%]	Dyspnea [%]	MCS [%]	STEMI [%]	NSTEMI [%]	PTCA [%]
Clift	2004	1	60	–	1 [100]	–	1 [100]	-	–
Harrison	2007	1	47	–	–	–	1 [100]	-	–
Acharya	2012	1	49	0	1 [100]	0	–	-	0
Kar	2012	1	67	0	0	0	–	-	–
Subban	2012	1	54	0	0	0	–	-	–
Acar	2013	1	48	0	1 [100]	0	1 [100]	–	–
Alkhouli	2015	1	71	1 [100]	1 [100]	0	1 [100]	0	0
Moriarty	2015	1	72	0	0	0	1 [100]	0	0
Singh	2015	1	82	0	1 [100]	0	1 [100]	0	1 [100]
Madan	2016	1	60	0	1 [100]	0	1 [100]	0	1 [100]
Nogueria	2016	1	81	0	0	0	1 [100]	0	0
Yudi	2017	1	79	0	0	0	1 [100]	0	1 [100]
Pavani	2018	1	65	0	0	0	1 [100]	0	1 [100]
Tang	2019	1	79	0	1 [100]	0	1 [100]	0	0
Bing	2020	3	78 [70–85]	1 [33]	–	1 [33]	–	–	1 [33]
Cavalcanti	2020	1	84	0	1 [100]	–	–	–	–
Gonzalez	2020	1	64	–	–	–	1 [100]	–	1 [100]
Total[#]		19	70 [47–85]	2 [13]	8 [57]	1 [8]	12 [100]	0	6 [23]

[#], percentage calculation for summary totals only include patients in studies directly reporting outcome of interest. MI, myocardial infarction; MCS, mechanical circulatory support; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PTCA, percutaneous transcatheter coronary angioplasty.

experiencing early mortality was 37.5% (95% CI: 29.0–46.8%, I^2=65%). On influence analysis, no studies were found to have excessive influence on outcome or between study heterogeneity. There was a suggestion of publication bias with an over-representation of patients experiencing low mortality on visual inspection of funnel plot (Figure S2A). Funnel plot asymmetry was statistically significant on Egger's test (P=0.037). Duval and Tweedie trim-and-fill method to correct for possible publication bias revealed an estimated proportion of patients experiencing early mortality of 53.3% (95% CI: 42.7–63.5%, I^2=79.5%), with an additional 10 imputed studies (Figure S2B). There was no identifiable impact of centre annual caseload on early mortality on meta-regression (P=0.654).

Procedural success

Procedural success was reliably reported in 21 studies (42-47,50,52-56,58-66). There were 43 failed procedures in 314 patients. The proportion of failed procedures was 15.9% (95% CI: 12.0–20.8%, I^2=0%). There were no overly influential studies on influence analysis. There was no evidence of publication bias on visual inspection of funnel plots (Egger's regression test, P=0.41). Presence of post-procedural shunt was reported in 15 studies (43,45,46,50,53,54,56-58,61-66). 21 out of 225 patients demonstrated a moderate or severe shunt at the time of discharge. The proportion of patients with a moderate or severe shunt was 13.8% (95% CI: 9.3–19.8%, I^2=0%). There were no overly influential studies. There was asymmetry evident on visual inspection of forest plots which was found to be significant on Egger's regression test (P=0.001) (Figure S3A). Trim-and-fill suggested the proportion of patients with a significant trans-septal shunt would be 18.2% (95% CI: 11.6–27.3%) after correction of

Table 7 Procedural outcomes and complications following percutaneous repair of LV free wall rupture

Author	Year	Patients (n)	Discharge (day) [range]	30 day-Mortality (%)	NYHA	Residual pseudoaneurysm (n)	Mortality at follow up [%]	Cause of death
Clift	2004	1	–	–	I	0	0	–
Harrison	2007	1		0	–	–	1	Recurrent PE
Archarya	2012	1	–	0	–	–	0	–
Kar	2012	1	–	0	–	–	0	–
Subban	2012	1	–	–	–	–	–	–
Acar	2013	1	5	–	–	–	–	–
Alkhouli	2015	1	–	0	–	–	0	–
Moriarty	2015	1	–	0	–	0	0	–
Singh	2015	1	3	0	I	0	0	–
Madan	2016	1	–	–	II	1 [100]	0	–
Nogueria	2016	1	–	0	–	–	0	–
Yudi	2017	1	–	–	–	–	–	–
Pavani	2018	1	–	–	–	–	–	–
Tang	2019	1	7	0	–	0	0	–
Bing	2020	3	–	–	–	–	0	–
Cavalcanti	2020	1	5	–	I	–	0	–
Gonzalez	2020	1	7	–	–	–	–	–
Total[#]		19	5 [3–7]	0	–	1 [20]	1 [7]	–

[#], percentage calculation for summary totals only include patients in studies directly reporting outcome of interest. LV, left ventricular; NYHA, New York Heart Association, heart failure grade; PE, pulmonary embolus.

publication bias, with 6 additional imputed studies (trim-and-fill funnel plot, Figure S3B).

Further procedures

Twenty studies (42-47,50,52-56,58-65) reported outcomes on the requirement of further procedures (both surgical and percutaneous), following percutaneous closure of post-infarct VSD. There were 46 patients out of 279 who required follow-up procedures. The proportion of patients requiring follow-up procedures was 19.3% (95% CI: 13.2–27.3%, I^2=38.6%). There were no overly influential studies. There was evidence of asymmetry on visual inspection of funnel plot confirmed on Egger's regression analysis (P=0.014) (Figure S4A). Trim-and-fill analysis suggests the proportion of patients requiring further procedures is 26.5% (95% CI: 18.2–36.7%) after correction of small study bias, with 7 additional imputed studies (trim-and-fill funnel plot, Figure S4B).

Impact of acuity on survival

The reported pooled average time for VSD diagnosis post-acute MI in 8 studies was 2.90 days (95% CI: 1.97–3.82 days, I^2=62.9%) (42-44,54,61,62,64). The time to VSD repair after diagnosis was reported in 17 studies as 22.0 days (95% CI: 12.4–31.6 days, I^2=99.4%) (43,44,46,49,50,52-56,59-62,64,66).

The outcomes of patient survival based on acuity of presentation was reported in 6 studies (42,46,54,56,58,59). There were 20 deaths in 31 patients presenting with acute post-infarct VSD and 6 deaths in 42 patients presenting with chronic post-infarct VSD. The risk ratio (RR) of mortality for patients with acute versus chronic post-infarct VSD

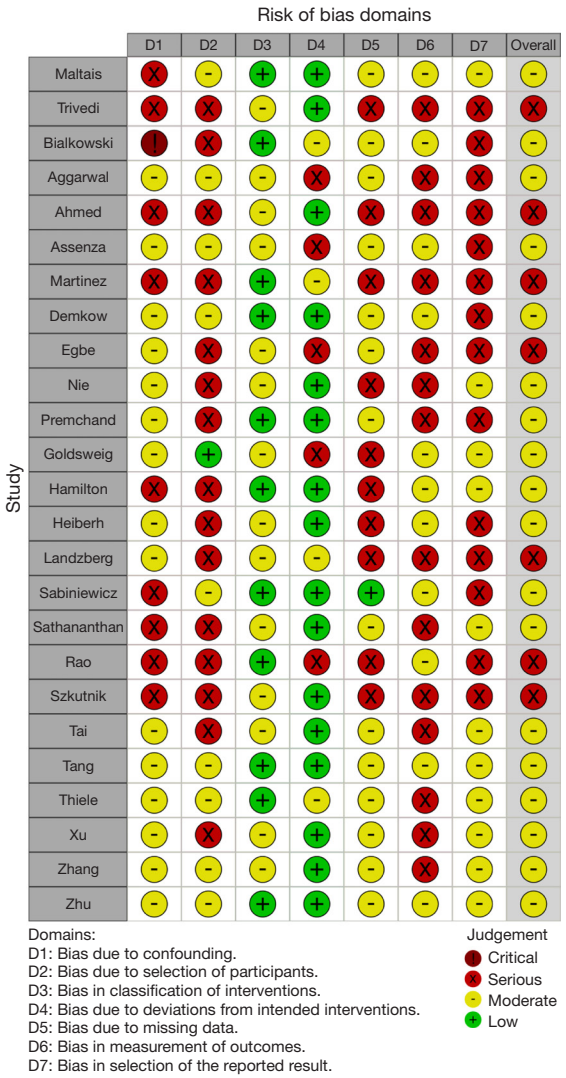

Figure 1 Risk of study bias assessment table for the treatment of post-MI ventricular septal defect. MI, myocardial infarction.

was 3.34 (95% CI: 1.2–9.0, P=0.026, I^2=8.8%) (*Figure 2*). The study by Sabiniewicz (56) was found to have an influential effect on the risk associated with the treatment of acute post-infarct VSDs. Exclusion of this study increased the RR to 5.07 (95% CI: 2.51–10.21, P<0.001, I^2=0%). Given the small study number, publication bias was unable to be formally assessed. Ten studies reported outcomes based on whether patients presented in cardiogenic shock. There were 39 deaths in 69 patients who presented with cardiogenic shock and, 18 deaths in 85 patients who presented in a stable condition. The RR of mortality between patients with cardiogenic shock compared to stable patients was 2.49 (95% CI: 1.71–3.63, P<0.001, I^2=0%) (*Figure 3*). There were no significantly influential studies, nor evidence of publication bias.

Discussion

The mechanical complications of ischemic heart disease are rare but devastating to the patients that suffer them. Acutely presenting patients often present critically unwell with significant morbidity and mortality associated with conventional surgical repair. This review has highlighted the emerging field of the percutaneous management of mechanical complications of IHD which, although having been practiced for several decades, remains in its infancy.

The early results of the treatment of PMR have encouraging results, with a low early mortality of 1 patient of the 42 reported cases. This low mortality contrasts with the reported early mortality for surgical intervention for PMR, which is 12.5–20% (67-69). However, the reported mortality for percutaneous mitral valve repair is almost certainly substantially underestimated through small study bias. The Japanese and American registry data reports the predominant mode of surgical intervention for PMR was mitral valve replacement in 79.8–90% (68,69), giving a reliable result. This review has demonstrated a significant minority (31%) of patients treated with percutaneous mitral repair were left with moderate or severe MR in a highly selectively reported group of patients. This review also demonstrates that the catastrophic and difficult to manage complications of LV FWR and LV free wall pseudoaneurysm can be managed in certain circumstances with percutaneous techniques. Although, this data is still very much case report based and thus, future study is certainly warranted.

The overall mortality of percutaneous repair of PMI-VSD reported in this study (37.5%) is similar to surgical outcomes of post-infarct VSD from various national registry data, ranging from 33.0–42.9% (70-72). This is despite a significant proportion of patients treated with primary percutaneous intervention being of prohibitive surgical risk. Only one study used percutaneous treatment as the preferred treatment, over surgical repair, for all patients presenting with PMI-VSD (62). However, the assessment of publication bias suggests overall mortality from percutaneous intervention is likely to be underestimated due to the presence of small study bias. The corrected estimated mortality was higher than reported surgical outcomes

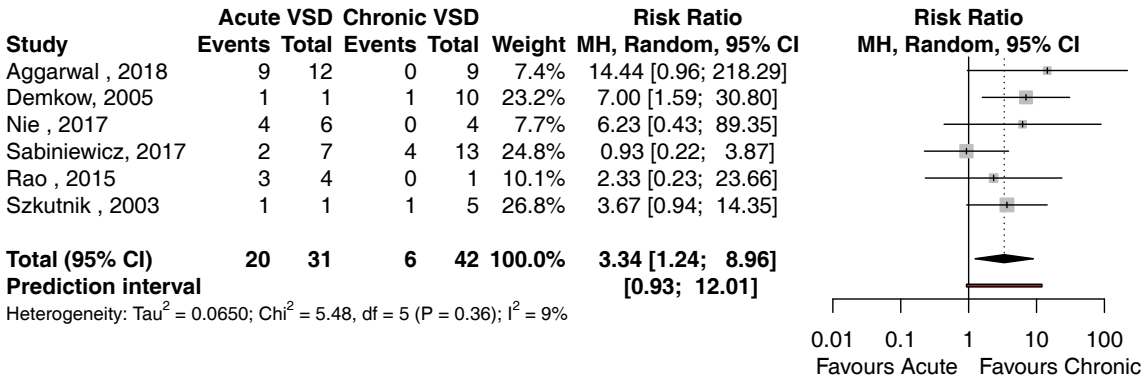

Figure 2 Forest plot demonstrating risk ratio of mortality of patients receiving treatment for acute versus chronic post-MI ventricular septal defect. CI, confidence interval; MH, Mantel-Haenszel method. MI, myocardial infarction.

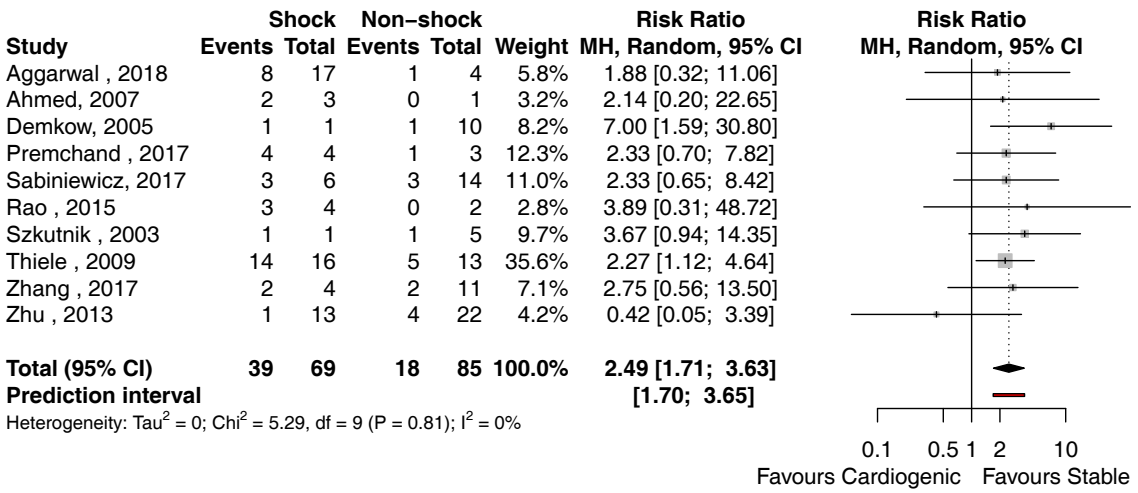

Figure 3 Forest plot demonstrating risk ratio of mortality of patients presenting in cardiogenic shock versus non-shock patients. CI, confidence interval; MH, Mantel-Haenszel method.

at 53.3%.

This manuscript highlights the increased risk that patients are at when they require early surgery. Acute surgery has been demonstrated to be high-risk for surgical intervention, for both PMI-VSD and PMR (68-72). Various strategies of prolonging time to surgery have been proposed including, the use of medical support with inotropes and mechanical assist devices, such as intra-aortic balloon pumps and extra-corporeal membrane oxygenation. Attempts have been made to provide extended periods of mechanical support to allow haemodynamic stabilization and an improvement in biochemical parameters prior to intervention. Mortality of patients requiring aggressive management with mechanical support to facilitate delayed surgical repair remains high, although a recent meta-analysis of published literature by Ronco and colleagues (73) assessed the surgical outcomes of 2,440 patients of whom 129 were treated with ECMO support prior to surgical repair. This study suggests a mortality benefit in patients treated with a prolonged period of stabilization using mechanical support compared to those operated on emergently. Currently, this strategy is not recommended to be utilised as a routine intervention for patients with post-infarct VSD who present in extremis although, mechanical cardiac support is recommended as a bridge to urgent repair (74).

Limitations

There are several important limitations with this analysis. All studies are of at least a moderate risk bias due to the small study size, retrospective analysis, absence of randomisation and implicit selection bias. There will be a substantial element of publication bias as well. However, this is an emerging field of technologies that is likely to expand with increased experience of all transcatheter and percutaneous interventions.

Conclusions

Mechanical complications of IHD are becoming an increasingly rare phenomenon due to advances in the management of coronary artery disease however, the associated mortality and morbidity remains high. Although surgical techniques remain the gold standard, we have shown that percutaneous management may be a viable option in certain cases. Further study and accurate reporting are clearly required to determine the true level of risk associated with these techniques, to ensure they are appropriately applied in these rare conditions.

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Footnote

Conflicts of Interest: The authors declare no conflicts of interest.

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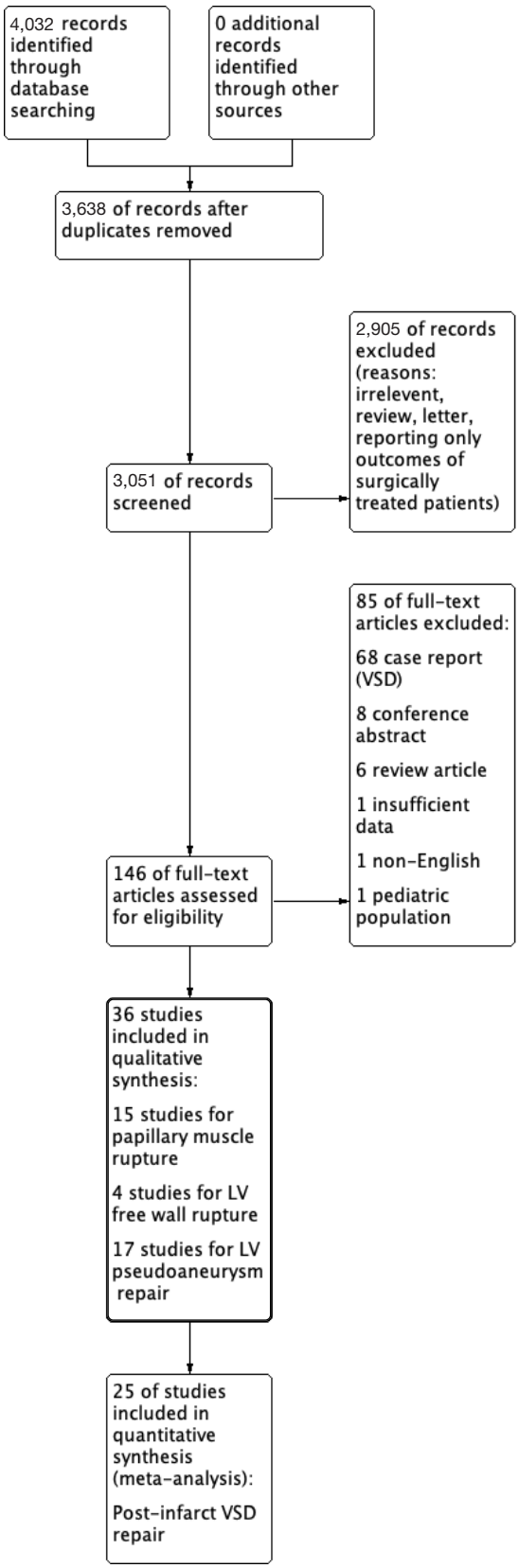

Figure S1 PRISMA diagram detailing search strategy.

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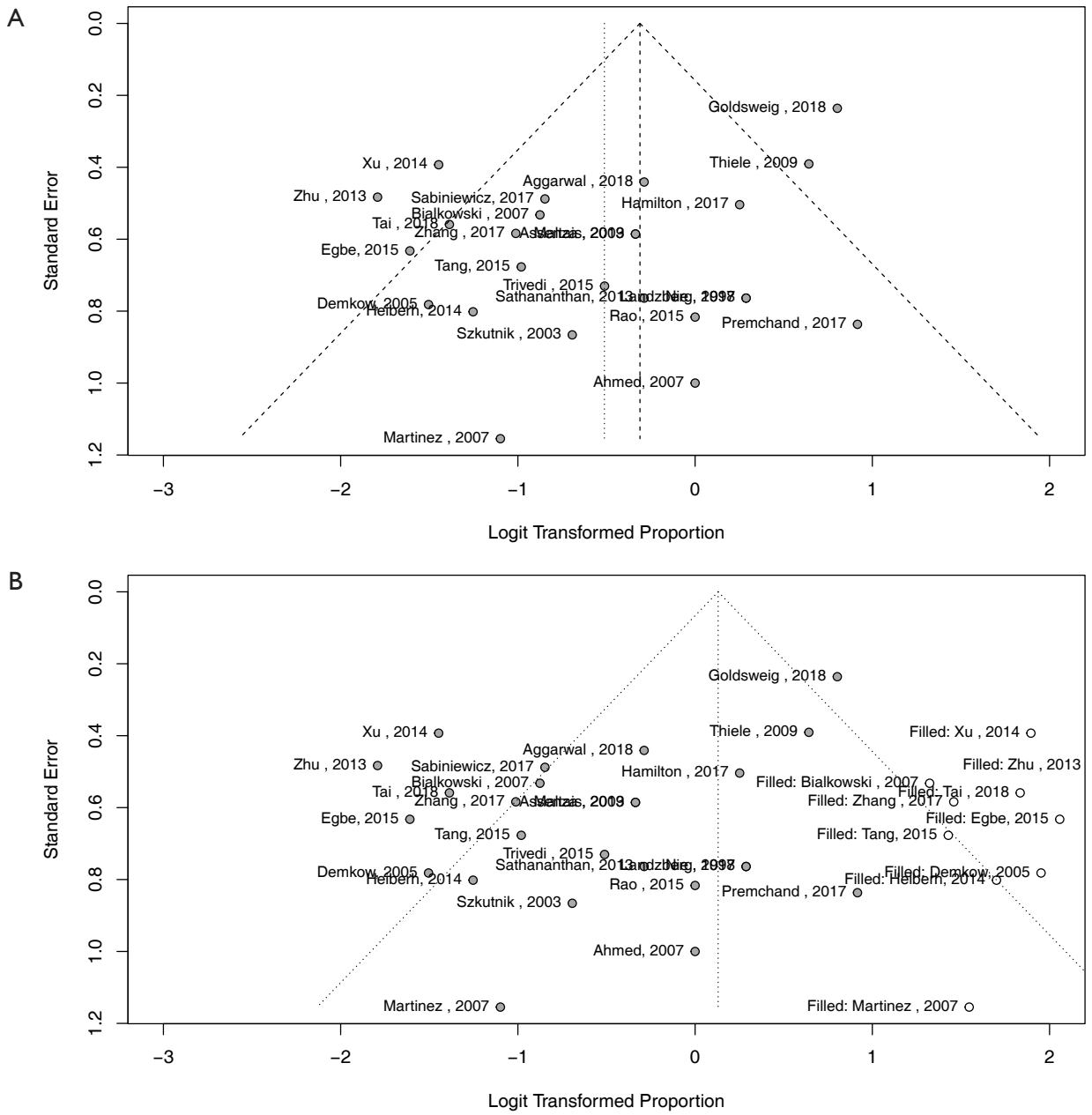

Figure S2 (A) funnel plot detailing results of mortality in patients receiving percutaneous treatment of post-MI VSD, (B) trim-and-fill funnel plot detailing results of mortality in patients receiving percutaneous treatment of post-MI VSD.

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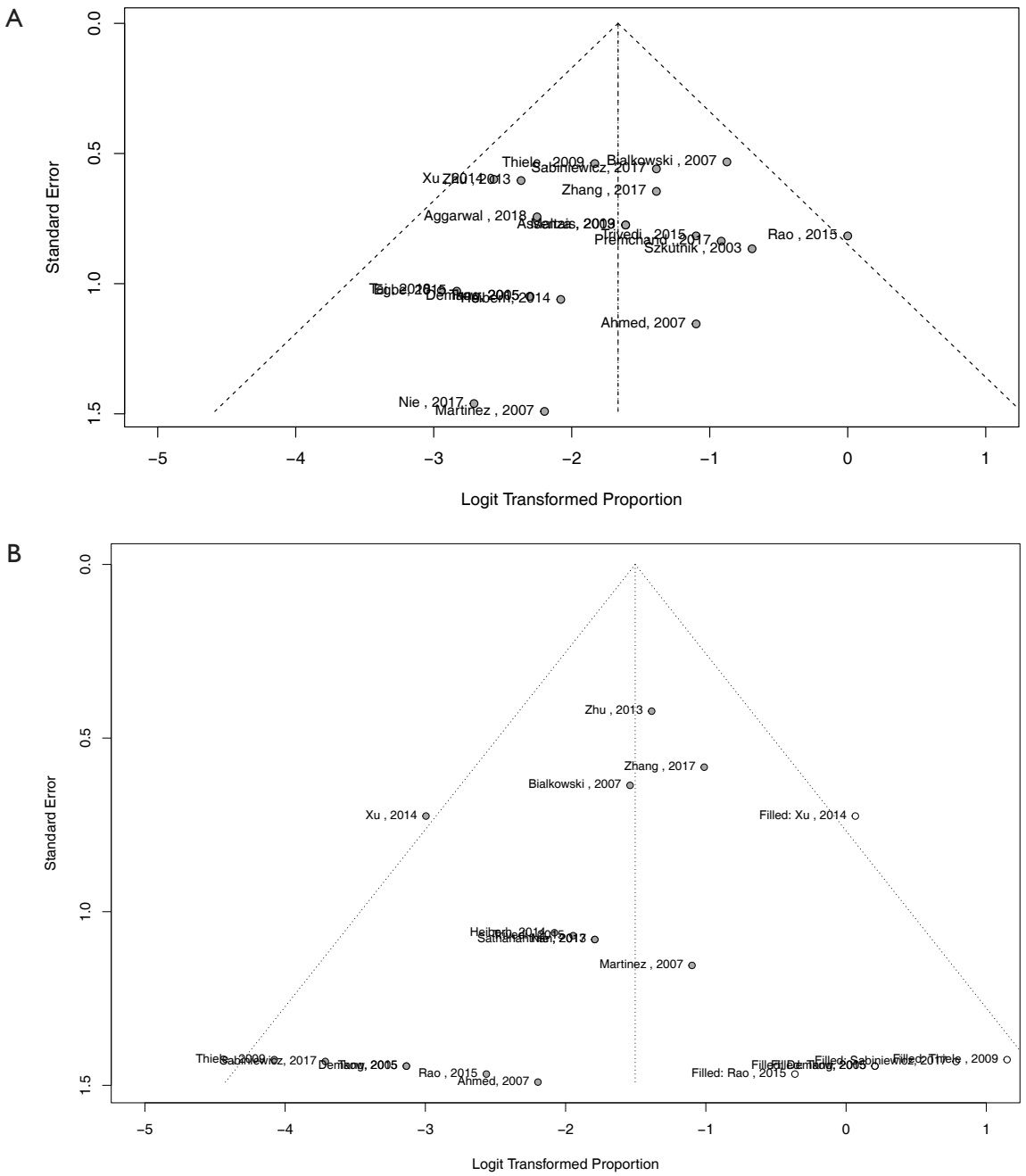

Figure S3 (A) funnel plot detailing outcomes of presence of significant residual trans-ventricular shunt in patients receiving percutaneous treatment of post-MI VSD, (B) trim-andfill funnel plot detailing results of presence of significant residual trans-ventricular shunt in patients receiving percutaneous treatment of post-MI VSD.

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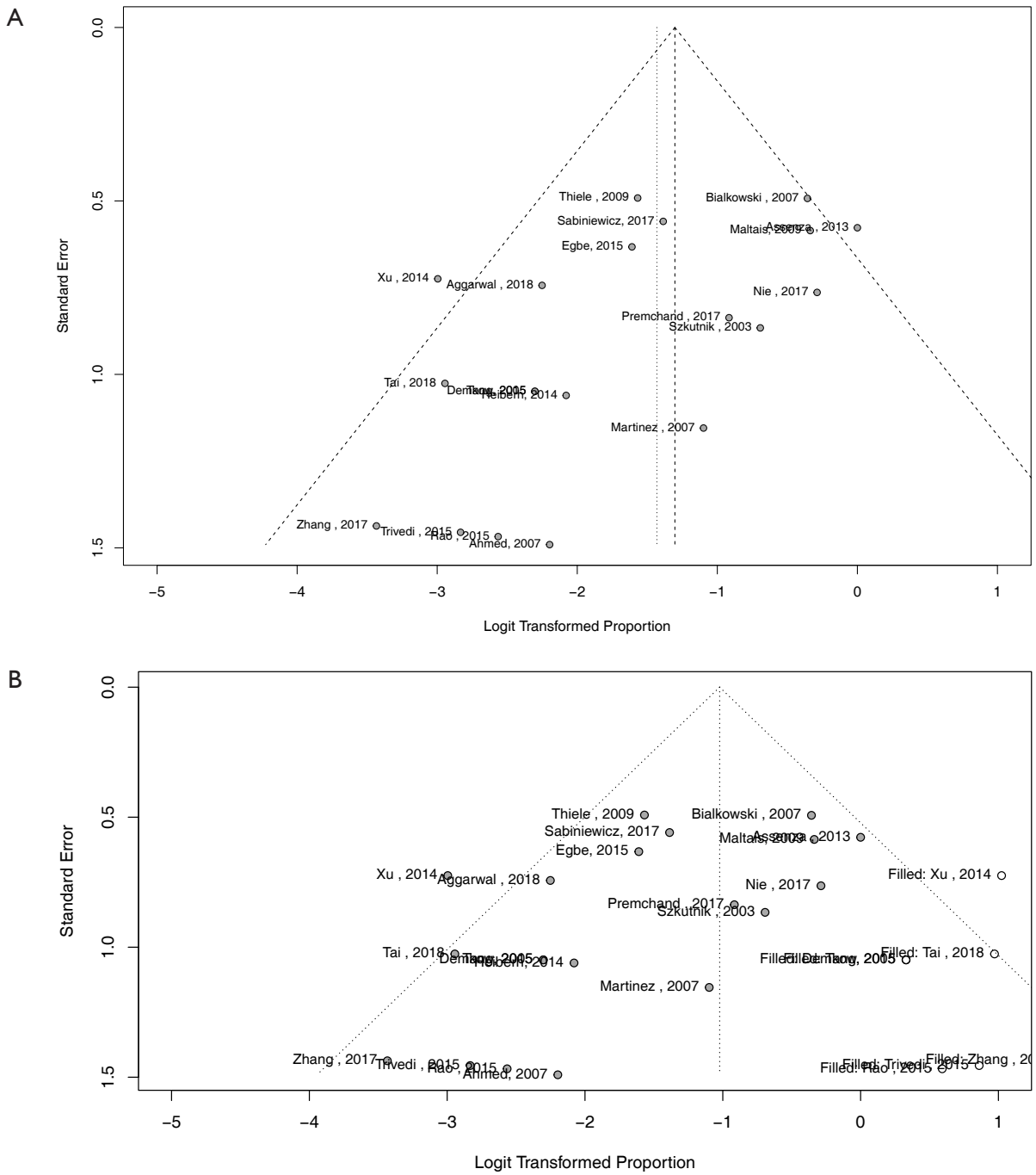

Figure S4 (A) funnel plot detailing outcomes of requirement for further procedures post-percutaneous treatment of post-MI VSD, (B) trimmed and filled funnel plot detailing outcomes of requirement for further procedures post-percutaneous treatment of post-MI VSD.

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