

# Comparison of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of perimembranous ventricular septal defects in children

## A PRISMA-compliant network meta-analysis of randomized and observational studies

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### Abstract

**Objective:** Our study was aimed to comprehensively compare the relative efficacy, safety, and the cost of transcatheter closure, mini-invasive closure, and open-heart surgical repair to treat perimembranous ventricular septal defects (pmVSDs) in children using network meta-analysis method.

**Methods:** Five databases were systematically searched including Chinese Biomedical Literature Database, China National Knowledge Infrastructure, PubMed, EMBASE.com, and the Cochrane Central Register of Controlled Trials from the starting date of each database to February 2017. Tools for assessing the risk of bias in nonrandomized studies of interventions (ROBINS-I) were used to evaluate the risk of bias in observational studies and Cochrane Handbook version 5.1.0 was used for randomized controlled trials (RCTs). Data were analyzed using R-3.4.0 software and Review Manager 5.2.

**Results:** Three RCTs and 24 observational studies were included in our study. Network meta-analysis result demonstrated that transcatheter closure was the most effective treatment in terms of operative time [standardized mean difference (SMD) = -2.02, 95% confidence interval (CI): -3.92 to -0.12], major complications [odds ratio (OR) = 0.52, 95% CI = 0.30-0.91], ICU stay (SMD = -1.11, 95% CI = -2.13 to -0.08), and hospital stay (SMD = -1.81, 95% CI = -2.24 to -1.39). However, open-heart surgical repair showed a higher success rate of the procedure than transcatheter closure (OR = 0.36, 95% CI = 0.17-0.77). Statistical analysis result demonstrated that transcatheter closure had the best potential to lessen major complications, ICU stay, hospital stay, operative time, and significant residual shunt.

**Conclusions:** Transcatheter closure has more benefit than mini-invasive closure and open-heart surgical repair to treat pmVSDs.

**Abbreviations:** CI = confidence interval, CHD = congenital heart disease, CPB = cardiopulmonary bypass, CrI = credible interval, OR = odds ratio, pmVSD = perimembranous ventricular septal defect, RCT = randomized controlled trial, SMD = standardized mean difference, VSD = ventricular septal defects.

**Keywords:** children, mini-invasive closure, network meta-analysis, open-heart surgical repair, perimembranous ventricular septal defects, transcatheter closure

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### 1. Introduction

Ventricular septal defect (VSD) is the most common type of congenital heart disease (CHD). Eighty percent of VSDs are perimembranous ventricular septal defects (pmVSDs).<sup>[1]</sup> Treatments for pmVSDs have been dramatically improved over the last 50 years.<sup>[2-4]</sup> Traditionally, open-heart surgical repair with midline sternotomy and cardiopulmonary bypass (CPB) was the primary approach to treat pmVSDs for many years. However, this approach is associated with relatively high morbidity, postoperative discomfort, and a large thoracotomy scar.<sup>[5]</sup> The catheter-based intervention was initially introduced for the closure of muscular VSDs and has been approved by the Food and Drug Administration in 2007.<sup>[6]</sup> It has become a promising alternative surgery approach to treat pmVSDs in developing countries, such as China and India.<sup>[7-9]</sup> But it is not currently approved for pmVSDs in the United States.<sup>[10,11]</sup> Moreover, it remains to be a challenge to use on children with low body weight.<sup>[10,12]</sup>

Previous pairwise meta-analysis suggested that there was no significant difference between transcatheter and surgical closure to treat pmVSDs in terms of early (up to 30 days) efficacy and safety in well-selected patients.<sup>[13]</sup> At the same time, the mini-invasive periventricular device occlusion technique, which combined the advantages of cardiac surgery, interventional cardiology, and medical image techniques guided by transesophageal echocardiography, was getting popular in application to treat VSDs and became a hotspot to study on in the basic medical research field.<sup>[14–17]</sup> However, there have been limited studies conducted to compare the efficacy among mini-invasive closure, transcatheter closure, and open-heart surgical repair for pmVSDs until now.

Therefore, we conducted a network meta-analysis, aiming to comprehensively compare the efficacy, safety, and costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair to treatment pmVSDs in children.

## 2. Methods

### 2.1. Registration and study protocol

This study was registered to the prospective international register of a systematic review (PROSPERO). The registration number is CRD42016053352. The protocol for this study was published in *BMJ Open*<sup>[18]</sup> (2017;7:e015642. doi:10.1136/bmjopen-2016-015642). The detailed methods could be found in published protocol.<sup>[18]</sup>

### 2.2. Search strategy

A systematic search was performed in 5 databases including Chinese Biomedical Literature Database, China National Knowledge Infrastructure, PubMed, EMBASE.com, and the Cochrane Central Register of Controlled Trials from their inception to February 2017. References of included articles and relevant systematic reviews were also tracked to identify other relevant studies. The search terms used in this study were thoracoscopic, sternotomy, minimally invasive, mini-invasive, surgical closure, transcatheter, perimembranous, and perimembranous.

### 2.3. Eligibility criteria

Randomized controlled trials (RCTs) and observational studies were included in the present work. For those included observational studies, the enrolled patients were younger than 18 years old and had pmVSDs confirmed by clinical and transthoracic echocardiographic. The patients were scheduled for transcatheter closure, mini-invasive closure, or open-heart surgical repair. The outcomes of interest included procedural success rate, operative time (minutes), ICU stay (hours), hospital stay (days), total cost, any residual shunt after procedure (residual shunt was defined as small if the width was  $\leq 2$  mm or significant if  $\geq 3$  mm<sup>[19]</sup>), major complications, and minor complications.<sup>[19]</sup>

### 2.4. Study selection and data extraction

Two reviewers independently selected studies and extracted data, any conflict was resolved by consulting with the third reviewer. Extracted data from selected studies included first author, year of publication, location, study design, study period, study arms,

sample, mean age, mean body weight, sex, VSD size, type of surgery, method of surgical closure, device used, mean device size, CPB time, median follow-up, and outcomes.

### 2.5. Risk of bias in individual studies

The risk of bias in the included observational studies was evaluated according to the tool for assessing risk of bias in nonrandomized studies of interventions (ROBINS-I),<sup>[20]</sup> the evaluated bias included bias due to confounding, bias due to missing data (postintervention), bias in measurement of outcomes (postintervention), bias in selection of participants into the study (preintervention), bias in classification of interventions (at intervention), bias due to deviations from intended interventions (postintervention), bias in selection of the reported result (postintervention), and overall risk of bias. We defined the risk of bias as low, moderate, serious, critical risk of bias, and no information.

The risk of bias tool from the Cochrane Handbook version 5.1.0 was used to evaluate the bias in the selected RCTs. The evaluated bias included a method of random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (detection bias), selective reporting (detection bias), and other bias.<sup>[21]</sup> We defined the risk of bias as low, high, or unclear risk of bias.

The risk of bias assessment was completed by 2 independent reviewers. A third reviewer was consulted if any conflicts occurred.

### 2.6. Statistical analysis

According to the published protocol,<sup>[18]</sup> we planned to perform a Bayesian network meta-analysis by using the package “*gemtc*” of R software. Since the measurement units of the interesting outcomes among included studies were different, we usually considered standardized mean difference (SMD) as treatment effects to analyze the results statistically. However, the package “*gemtc*” could not perform the calculation of treatment effects of SMD.<sup>[22]</sup> Thus, we changed to perform a Frequentist network meta-analysis using package “*netmeta*” 3.4.1 of R-software 4.1.0 in the present review.<sup>[23]</sup>

The “*decomp.design*” function was used to assess the homogeneity of the whole network, the homogeneity within designs, and the homogeneity/consistency between designs. Posterior medians of odds ratio (OR) with 95% credible intervals (CrIs) were used for procedural success rate, significant residual shunt, major complications, and minor complications. SMDs with 95% CrI for operative time, ICU stay, hospital stay, and total cost. In addition, the *P* scores based on the point estimates or standard errors of the network estimates were used to conduct treatment ranking. *P* score rankings were calculated and used to indicate the probability of each treatment to be best.<sup>[24]</sup> Inconsistency between direct and indirect comparisons was evaluated by a node splitting method.<sup>[25]</sup>

## 3. Results

### 3.1. Baseline characteristics of included studies

We initially identified 927 potentially eligible studies, after the titles and abstracts reviewing, 796 studies were excluded. One hundred thirty-one studies were left for further reviewing. Finally, 27 studies met our inclusion criteria (Appendix 1, [2](http://</a></p>
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links.lww.com/MD/C517). The flowchart of literature selection is shown in Figure 1.

The final selected 27 studies included 3 RCTs and 24 observational studies. The mean study period was 2.8 years (ranging from 1 to 12 years). For the intervention of open-heart, 16 studies with a total of 1938 patients received median sternotomies under CPB. A total of 6421 patients with pmVSDs were included in our study. The mean age of patients in each study ranged from 6.1 months to 21.16 years old, and the mean body weight ranged from 8.58 to 49.62 kg.

Only 3 types of intervention were included in our study: transcatheter, open-heart, and mini-invasive. Twenty-two studies including 4941 patients received the intervention from transcatheter and open heart. Only 4 studies including 1345 patients received the mini-invasive intervention, and 1 study including 126 patients received transcatheter and mini-invasive. Baseline characteristics of the included studies are shown in Table 1.

**3.2. Risk of bias for individual studies**

The results of the risk of bias evaluation for all included studies were presented in Appendix 2, <http://links.lww.com/MD/C517>.

All included studies were categorized as low risk in bias in terms of confounding bias, bias in emulsification of interventions, bias due to deviations from intended interventions, and bias in the measurement of outcomes. All studies were classified as no information in the bias of selection of participants into the study. Fourteen studies showed a low risk of bias due to missing data. Three studies showed a low risk in the bias of selection of the reported result. Three studies were assessed as low risk in bias in terms of overall risk of bias (Table 2).

**3.3. Network meta-analysis**

The heterogeneity assessment results among studies and the whole network could be found in Appendix 3, <http://links.lww.com/MD/C517>. We conducted both a direct (Appendix 3, <http://links.lww.com/MD/C517>) and a network meta-analysis (Table 3) for the efficacy of 3 treatments on patients with pmVSDs. Both direct and network evidence showed that transcatheter closure had lower major complications than open heart [OR=0.52, 95% confidence interval (CI)=0.30–0.91], whereas the procedural success rate of open heart was higher than transcatheter closure (OR=0.36, 95% CI=0.17–0.77). However, ICU stay,

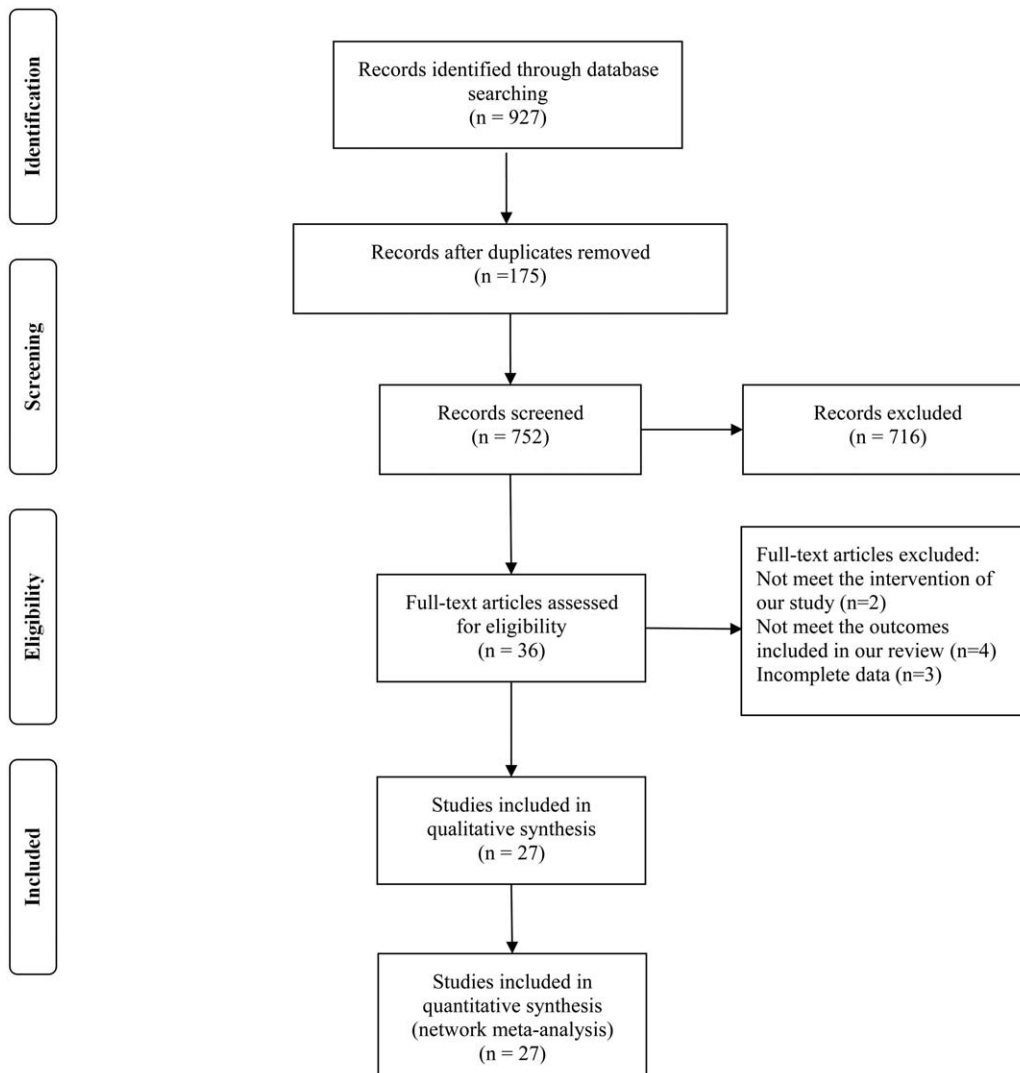


Figure 1. The diagram of literature selection procedure.

**Table 1****Baseline characteristics of included studies.**

Author	Country	Design	Intervention	Sample N/M/F	VSD size, mm	Type of surgery
Hu HB, 2004	China	Observation	Transcatheter	45/22/23	5.0 ± 1.2	
			Open-heart	45/21/24	5.1 ± 1.4	Median sternotomy with CPB
Xiao YQ, 2008	China	Observation	Transcatheter	20/9/11	5.57 ± 1.34	
			Open-heart	20/11/9	6.08 ± 1.77	Median sternotomy with CPB
Xu XL, 2014	China	Observation	Transcatheter	200/108/92	6.78 ± 3.85	
			Open-heart	105/54/51	6.45 ± 2.76	Median sternotomy with CPB
Zhang CG, 2013	China	Observation	Transcatheter	82/32/50	5.16 ± 1.31	
			Open-heart	56/26/30	5.53 ± 1.60	Median sternotomy
Song JD, 2015	China	Observation	Transcatheter	182/112/70	4.0 ± 2.5	
			Open-heart	202/108/94	5.0 ± 2.08	Median sternotomy with CPB
Li K, 2011	China	Observation	Transcatheter	185/128/57	4.52 ± 3.31	
			Open-heart	200/132/68	4.67 ± 2.67	Median sternotomy with CPB
Qu X, 2005	China	Observation	Transcatheter	48/33/15	3.87 ± 1.66	
			Open-heart	73/51/22	7.39 ± 4.08	CPB
Zhang H, 2006	China	Observation	Transcatheter	174/90/84	5.15 ± 1.88	
			Open-heart	78/37/41	13.06 ± 6.48	CPB
Dai FF, 2013	China	Observation	Transcatheter	55/26/29	3.33 ± 1.40	
			Open-heart	105/66/39	8.48 ± 3.73	Median sternotomy with CPB
Shang XK, 2014	China	Observation	Transcatheter	88/38/50	7.22 ± 2.36	
			Open-heart	141/59/82	7.46 ± 1.94	Median sternotomy with CPB
Zhang Y, 2013	China	Observation	Transcatheter	45/22/23	4.0 (3.0–13.0)	
			Mini-invasive	81/45/36	5.0 (2.7–11.0)	Median sternotomy with CPB
Wang J, 2015	China	Observation	Transcatheter	61/29/32	-	
			Open-heart	48/27/21	-	Median sternotomy with CPB
Xue YB, 2016	China	Observation	Transcatheter	100/58/42	-	
			Open-heart	100/57/43	-	Median sternotomy with CPB
Zhang XQ, 2015a	China	RCT	Mini-invasive	265/138/127	7.05 ± 2.42	
			Open-heart	265/136/129	7.24 ± 2.32	Left lateral recumbent right axilla
Zhang YZ, 2011	China	Observation	Mini-invasive	85/48/37	6.3 ± 3.6	
			Open-heart	80/45/35	8.8 ± 5.3	Median sternotomy with CPB
Xu PF, 2011	China	Observation	Transcatheter	408/198/210	5.27 ± 3.04	
			Open-heart	440/243/197	13.24 ± 5.0	Median sternotomy with CPB
Wang XY, 2007	China	Observation	Transcatheter	53/30/23	-	
			Open-heart	50/28/22	-	Median sternotomy with CPB
Chen Q, 2014	China	Observation	Transcatheter	89/38/51	7.6 ± 1.6	
			Open-heart	58/27/31	-	Standard technique under CPB
Zhang XQ, 2015b	China	RCT	Mini-invasive	265/138/127	7.02 ± 2.42	
			Open-heart	265/136/129	7.24 ± 2.32	The right subaxillary straight incision
Cheng XM, 2007	China	Observation	Transcatheter	73/24/49	4.8 ± 2.28	
			Open-heart	48/10/38	8.2 ± 2.25	Median sternotomy
Hu YJ, 2014	China	Observation	Mini-invasive	96/42/54	4.2 ± 1.8	
			Open-heart	33/15/18	5.1 ± 2.2	Right infra-axillary thoracotomy
Liu SX, 2012	China	Observation	Transcatheter	157/64/93	4.1 ± 1.4	
			Open-heart	188/96/92	6.3 ± 4.1	Median sternotomy with CPB
Oses P, 2010	China	Observation	Transcatheter	37/16/21	10.9 ± 7.4	
			Open-heart	34/19/15	8.5 ± 2.6	Median sternotomy with CPB
Xu F, 2012	China	Observation	Transcatheter	89/42/47	5.1 ± 1.5	
			Open-heart	97/48/49	6.4 ± 1.7	Median sternotomy
Yang J, 2014	China	RCT	Transcatheter	101/50/51	NA	
			Open-heart	99/61/38	NA	Median sternotomy with CPB
Chen ZY, 2014	China	Observation	Transcatheter	81/37/44	4.1 ± 1.2	
			Open-heart	115/60/55	4.3 ± 1.3	Right lateral thoracotomy with CPB
Luo YK, 2015	China	Observation	Transcatheter	172/101/71	4.5 ± 1.6	
			Open-heart	139/69/70	4.6 ± 2.4	Right side

CPB = cardiopulmonary bypass, RCT = randomized controlled trial.

hospitalization, and operative time of transcatheter closure were less than those of open heart (SMD = -1.11, 95% CI = -2.13 to -0.08; SMD = -1.81, 95% CI = -2.24 to -1.39; SMD = -3.21, 95% CI = -4.28 to -2.14, respectively). The operative time of mini-invasive was not significantly different from that of

transcatheter indirect meta-analysis ( $P > .05$ ), whereas network meta-analysis result demonstrated that transcatheter had less operative time than mini-invasive (SMD = -2.02, 95% CI: -3.92 to -0.12). There was no significant difference in terms of other outcomes (all  $P > .05$ ).

**Table 2**  
Results of network meta-analysis.

Comparisons	Major complication	Procedural success rate	Significant residual shunt	Hospital stay	ICU stay	Operative time	Total cost	Minor complication
Mini-invasive (reference)								
Open-heart	OR: 1.27 (0.46–3.46)	OR: 2.32 (0.54–9.95)	OR: 1.00 (0.19–5.21)	–	–	SMD: 1.08 (–0.61–2.78)	SMD: 1.20 (–0.67–3.07)	–
Transcatheter	OR: 0.60 (0.20–1.80)	OR: 0.79 (0.16–3.85)	OR: 0.92 (0.14–6.00)	<b>SMD: –1.38</b> (–2.30 to –0.46)	SMD: –0.38 (–1.74–0.98)	<b>SMD: –2.02</b> (–3.92 to –0.12)	–	–
Open-heart (reference)								
Transcatheter	<b>OR: 0.47</b> (0.27–0.82)	<b>OR: 0.34</b> (0.16–0.72)	OR: 0.02 (0.29–2.94)	–	–	<b>SMD: –3.11</b> (–4.15 to –2.06)	–	OR: 0.68 (0.32, 1.43)

Bold values are statistically significant.  
ICU = intensive care unit.

**Table 3**  
P score ranking results.

Treatments	Major complication	Procedural success rate	Significant residual shunt	Hospital stay	ICU stay	Operative time	Total cost	Minor complication
Mini-invasive	0.4286	0.3727	0.4819	0.418	0.6191	0.4566	<b>0.8188</b>	–
Open-heart	0.1636	<b>0.9347</b>	0.4703	0.418	0.0359	0.0526	0.5897	–
Transcatheter	<b>0.9078</b>	0.1926	<b>0.5478</b>	<b>0.9969</b>	<b>0.845</b>	<b>0.9908</b>	0.0914	–

Bold values are the top one value of P score ranking.  
ICU = intensive care unit.

### 3.4. Ranking results

P score ranking result (Table 3) showed that transcatheter closure was ranked the top one in major complications, ICU stays, hospital stay, operative time, and significant residual shunt (P score = .9078, .8450, .9969, .9908, .5478, respectively). For procedural success rate, open-heart was ranked the top one (P score = .9347). Mini-invasive was top one in terms of total cost (P score = .8188).

### 3.5. Inconsistency between direct and indirect comparisons

Assessment of inconsistency between direct and indirect comparisons was performed by using the node-splitting model, and the results showed that there was no inconsistency among all included studies (all P > .05). The results of inconsistency analysis are presented in Appendix 4, <http://links.lww.com/MD/C517>.

### 3.6. Sensitivity analysis

We performed a sensitivity analysis of the 3 RCTs. The results are presented in Appendix 4, <http://links.lww.com/MD/C517>. Statistically significant differences were found between mini-invasive and transcatheter closure, and between mini-invasive and open-heart for outcomes of significant complications, operative time, hospital stay, and total cost. The pooled results of 3 RCTs suggested that mini-invasive had less major complications (OR = 2.81, 95% CI = 1.81–4.36), shorter operative time (SMD = 3.88, 95% CI = 3.68–4.09), less total cost (SMD = 3.10, 95% CI = 2.92–3.28), and shorter hospital stay (SMD = 2.57, 95% CI = 2.21–1.93) than open heart. Mini-invasive also had lower total cost than transcatheter (SMD = 2.06, 95% CI = 1.71–2.41).

## 4. Discussion

Presently, a large number of children with different types of CHDs are waiting to be treated. PmVSDs account for approximately one fifth of all defects of CHDs. To the best of our knowledge, there are no relevant RCTs to comprehensively compare the differences between transcatheter closure, mini-invasive closure, and open-heart surgical repair to treat pmVSDs. For the first time, our study compared the efficacy, safety, and the costs of transcatheter closure, mini-invasive closure, and open-heart surgical repair for treatment of pmVSDs in children. The results showed that transcatheter closure had shorter operative time than mini-invasive and open-heart. Compared to open-heart, transcatheter closure also demonstrated lower major complications, shorter ICU stay, and shorter hospital stay. In contrast, open-heart had higher procedural success rate than transcatheter closure. Network meta-analysis incorporating direct and indirect evidence demonstrated that transcatheter closure had the most considerable benefit regarding to the operative time, major complications, ICU stay, and hospital time. According to the P score ranking, transcatheter closure ranked the top 1 in terms of major complications, ICU stays hospital stay, operative time, and significant residual shunt.

Surgery repair has been regarded as the “criterion standard” for treatment of pmVSDs for many years. Hijazi et al<sup>[26]</sup> firstly closed pmVSDs by using an Amplatzer occluder in 2002. Although Yang’s study found that the Amplatzer occlude was associated with a relatively high risk of the complete atrioventricular block over the past decade.<sup>[27]</sup> Interest has been grown in developing new techniques that could replace traditional open-heart surgery to treat pmVSD.<sup>[27]</sup> Although transcatheter is still being considered as a challenging procedure to treat pmVSDs due to the close association of pmVSDs to the aortic and tricuspid valve apparatus, atrioventricular conduction system, and left

ventricular outflow tract closely, the outcomes of using the transcatheter procedure to treat pmVSDs have been improved significantly in recent years.<sup>[3,28]</sup> Recent RCT studies demonstrated that both transcatheter device closure and surgical repair were effective treatments to pmVSDs in children with excellent midterm outcomes.<sup>[27]</sup> Quek's study showed that transcatheter had some unique advantages (e.g., shorter hospital stay, shorter recovery time, avoidance of the need of CPB, lower complications rate relating to surgery, and reduced psychological impact). And 1 RCT suggested that using transcatheter intervention could technically make it easier to repair window, tubular, and infundibular types of pmVSDs and had fewer complications.<sup>[27]</sup>

One study suggested that the total cost of transcatheter was higher than open-heart surgery.<sup>[29]</sup> The higher cost of transcatheter attributed to the remote electrocardiogram monitoring of patients in the hospital for 6 to 7 days and the use of occluder. This study revealed that there was no significant difference between the 2 groups for the time of hospital stay. However, our network meta-analysis showed that transcatheter had shorter hospital stay time than open-heart surgery and no statistically significant differences in terms of total cost were found between these 2 groups either.

One distinct advantage of our systematic review was that both direct and indirect evidence were used to compare that the outcomes of transcatheter, open-heart, and mini-invasive simultaneously. However, there were some limitations in our meta-analysis as well. Firstly, the costs for each intervention were not reported in most of the selected studies, and it varies over time and regionally. All these factors contributed to the inconsistency in each intervention technique cost and led to a certain extent of bias. Secondly, in the United States, implantation is performed by cardiologists. However, in other countries, general surgeons or the radiologist implants the devices for patients. Because of the different pay rates for cardiologists and general surgeons, the surgical costs may be cheaper than the device closure in some countries. Finally, the results of sensitivity analysis only for RCT studies showed that the statistical differences in some outcomes changed from no significant differences to significantly different. However, the number of included RCTs in our studies was extremely small (only 3). More high-quality RCTs are needed to get a more reliable result.

In conclusion, transcatheter closure showed more benefits than mini-invasive and open-heart interventions in the treatment of pmVSDs. However, only 3 RCTs were included in our study, and more RCTs with high-quality data are wanted to make a better understanding.

### Author contributions

Conception and design of research (YT, YK, DZH, HXD, TJH); tested the feasibility of the study (YT, YK, LXG, WXX); searched databases (TJH); studies selection and data collection (YT, YK, DZH, HXD, LXG, WXX); analyzed data (YK, TJH); wrote the manuscript (YT); approved the final manuscript (YT, TJH).

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**Methodology:** Tao You, Jin-hui Tian.

**Project administration:** Tao You, Zhao-hong Ding, Xiao-dong Hou.

**Software:** Jin-hui Tian.

**Validation:** Kang Yi.

**Visualization:** Kang Yi.

**Writing – original draft:** Kang Yi, Tao You.

**Writing – review and editing:** Kang Yi, Tao You, Zhao-hong Ding, Xiao-dong Hou, Xing-guang Liu, Xin-kuan Wang.

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