Pericardial effusion after congenital heart surgery

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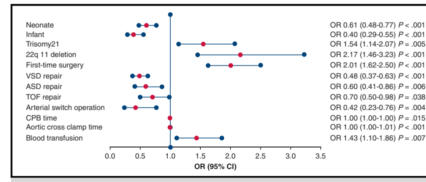
ABSTRACT

Objective: Pericardial effusion after cardiac surgery remains an important cause of morbidity and mortality. We describe the risk factors of pericardial effusion after congenital heart surgery through analyzing data from a nationwide, multi-institutional registry.

Methods: The Japan Congenital Cardiovascular Surgery Database, which reflects routine clinical care in Japan, was used for this retrospective cohort study. Multivariable regression analysis was done after univariable comparison of patients with pericardial effusion and no pericardial effusion.

Results: The study enrolled 64,777 patients registered with the Japan Congenital Cardiovascular Surgery Database between 2008 and 2016; 909 of these had postoperative pericardial effusion (1.4%) and were analyzed along with 63,868 patients without pericardial effusion. Univariable analysis found no difference between the groups in terms of gender, early delivery, or preoperative mechanical ventilatory support. In the pericardial effusion group, cardiopulmonary bypass use was lower (58.4% vs 62.1%), whereas the cardiopulmonary bypass time (176.9 vs 139.9 minutes) and aortic crossclamp time (75.1 vs 62.2 minutes) were longer, and 30-day mortality was higher (4.1% vs 2.2%). Multivariable analysis identified trisomy 21 (odds ratio, 1.54), 22q.11 deletion (odds ratio, 2.17), first-time cardiac surgery (odds ratio, 2.01), and blood transfusion (odds ratio, 1.43) as independent risk factors of postoperative pericardial effusion. In contrast, neonates, infants, ventricular septal defect, atrial septal defect, tetralogy of Fallot repair, and arterial switch operation were correlated with a low risk of pericardial effusion development.

Conclusions: The incidence of postoperative pericardial effusion in congenital cardiac surgery was 1.4%. Trisomy 21, 22q.11 deletion, first-time cardiac surgery, and blood transfusion were identified as the principal factors predicting the need for pericardial effusion drainage. (JTCVS Open 2022;9:237-43)



PE after congenital cardiovascular surgery; final multivariable model.

CENTRAL MESSAGE

Trisomy 21, 22q.11 deletion, first-time cardiac surgery, and blood transfusion are major factors in predicting the need for drainage of PE after congenital heart surgery.

PERSPECTIVE

PE after cardiac surgery remains a cause of morbidity and mortality because its occurrence is difficult to predict. Analysis of data from a multi-institutional clinical registry found trisomy 21, 22q.11 deletion, first-time cardiac surgery, and transfusion as risk factors. Postoperative PE may be predicted by assessing these risk factors and prevented by minimizing blood transfusions.

See Commentary on page 244.

Pericardial effusion (PE) after cardiac surgery remains an important cause of morbidity and mortality because it can lead to significant hemodynamic consequences, such as cardiac tamponade. Recent reports indicated that postoperative PE has a prevalence of 1.1% to 23% in pediatric or congenital cardiac surgery.[1-4] It has often been claimed that postoperative PE is a component of postpericardiotomy syndrome (PPS), currently considered to be an immune-mediated inflammatory process triggered by surgical trauma to the pericardium, and is associated with a late onset of complications and sudden manifestation of symptoms. Its pathophysiology has not been definitively proven, and there are still no widely recognized or confirmed risk factors despite numerous reports of various candidate risk factors. Because both the etiology and the clinical risk factors of PE are still unclear, its complications remain difficult to predict. Therefore, the present study aimed to describe the risk factors of PE after congenital heart surgery using the Japan Congenital Cardiovascular Surgery Database (JCCVSD), a nationwide registry of almost all Japanese cardiovascular hospitals that provides

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Abbreviations and Acronyms

ASD = atrial septal defect
CPB = cardiopulmonary bypass
JCCVSD = Japan Congenital Cardiovascular Surgery Database
OR = odds ratio
PA = pulmonary artery
PE = pericardial effusion
PPS = postpericardiotomy syndrome
TOF = tetralogy of Fallot
VSD = ventricular septal defect

data for use in nationwide health quality assessments and clinical research.

MATERIAL AND METHODS

Data Source

The JCCVSD was used for the present retrospective cohort study. Variables and definitions used in the JCCVSD are almost identical to those of the Society of Thoracic Surgeons European Association for Cardiothoracic Surgery database for congenital heart surgery.[5] The JCCVSD began collecting data in 2008 and developed into a nationwide database by 2011, with data being collected from 121 facilities covering almost all medical centers where congenital cardiovascular surgery is performed in Japan. Currently, detailed information on more than 10,000 patients is recorded in the registry annually, including preoperative, operative, and outcome data. Analytical reports from the database are highly representative of routine clinical care in Japan. Approval for the present study was obtained from the Institutional Review Board at Tokyo Metropolitan Children's Medical Center (No. 2019b-54, 09/04/2019), and use of the data was approved by the JCCVSD ethics committee. Institutional Review Board provided a waiver of informed consent from the patients.

Study Population

All congenital heart surgeries registered in the JCCVSD between January 1, 2008, and December 31, 2016, were eligible for inclusion. The study population consisted of 64,777 patients. For multivariable regression analysis, the cohort was limited to 38,702 patients with a complete set of data, including all the variables listed in Table 1. All patients were counted once even if multiple instances of postoperative PE occurred in a single individual.

Data Collection and Definitions

Postoperative PE was defined as (1) postoperative PE requiring drainage or (2) PE or tamponade requiring readmission within 30 days postoperatively, both of which are categories in the case report form in the JCCVSD. Patients with postoperative hemorrhage or mediastinitis were excluded from the postoperative PE population. Data collected from the total cohort included gender, age, and weight at cardiac surgery, chromosomal abnormalities, early delivery, and use of preoperative mechanical ventilatory support as the basic, preoperative characteristics. Information about previous cardiac surgery was also included. Ventricular septal defect (VSD) repair, atrial septal defect (ASD) repair, systemic to pulmonary artery (PA) shunt, PA banding (PA banding, excluded bilateral procedures), Fontan procedure, bidirectional Glenn procedure, tetralogy of Fallot (TOF) repair, atrioventricular septal defect repair, arterial switch operation, and double outlet right ventricular repair were included among the operative variables as the 10 most common surgical procedures. Cardiopulmonary bypass (CPB) use and its duration, aortic crossclamp time, and blood transfusion were investigated as operative data, and 30-day mortality was included in the outcome data.

Statistical Analysis

Categorical variables were described in terms of absolute count and relative frequency (percentages). The data were normally distributed. Continuous variables were presented as the mean ± standard deviation. Pearson's chi-square test and Welch's t test were used to test for the statistical significance of the univariable association between each variable and postoperative PE. A multivariable logistic regression model was created to determine the influence of each risk factor, and odds ratios (ORs) were calculated with 95% confidence intervals. Forward stepwise selection with P for entry .05 and P for removal .10 was used. All analyses were performed using SPSS Statistics software (version 26, IBM SPSS Inc, Armonk, NY).

RESULTS

In total, 64,777 patients in the JCCVSD between January 1, 2008, and December 31, 2016, were enrolled. There were 909 patients with postoperative PE during the study period, for an incidence of 1.4%.

Univariable Comparison of Patients With Pericardial Effusion and No Pericardial Effusion

All patients, including the 909 patients with PE and the 63,868 patients without PE, were evaluated. All the variables in the basic characteristics and the preoperative, operative, and outcome data were compared between the 2 groups (Table 1). The male-to-female ratio was similar for both groups and showed no significant difference. Age at cardiac surgery was classified into 3 categories: neonates (age ≤28 days), infants (28 days < age <365 days), and older (365 days ≤ age). Body weight at cardiac surgery was also divided into 3 categories: BW <2.5 kg, 2.5 kg ≤ BW <3.0 kg, and 3.0 kg ≤ BW. The details are summarized in Table 1. The 3 major chromosomal abnormalities of trisomy 21, 22q.11 deletion, and trisomy 18 were investigated. The percentage of patients with no chromosomal abnormality was 77.9% in the PE group and 87.1% in the no PE group. Early delivery, defined as delivery at less than 37 weeks of gestation, did not differ significantly between the groups. Preoperative mechanical ventilatory support to treat cardiorespiratory failure did not differ between the groups. Incidence of first-time cardiac surgery was higher in the PE group than in the no PE group (PE 66.9% vs no PE 62.1%; $P = .003$). The 10 most common surgical procedures were investigated (Figure 1). Figure 1 shows the prevalence of each procedure and the frequency of postoperative PE per procedure type. Although the proportion of PA banding among the procedures in the entire patient cohort was not high (5.9%), PA banding had the highest proportion (12.8%) among patients with PE. CPB use was lower (PE 58.4% vs 62.1%; $P = .010$), CPB time (PE 176.9 vs 139.9 minutes; $P < .001$) and aortic crossclamp

TABLE 1. Baseline characteristics and perioperative data on patients with pericardial effusion and no pericardial effusion after congenital cardiovascular surgery

Characteristic	PE n = 909 (%)	No PE n = 63,868 (%)	*P* value
Male	490 (53.9)	33,394 (52.3)	.761
Age at cardiovascular surgery			<.001
Age ≤28 d (neonate)	361 (39.7)	24,337 (38.1)	
28 d < age <365 d (infant)	95 (10.5)	10,668 (16.7)	
365 d ≤ age	453 (49.8)	28,863 (45.2)	
Weight at cardiovascular surgery			.017
BW <2.5 kg	65 (7.2)	5468 (8.6)	
2.5 kg ≤ BW <3.0 kg	92 (10.1)	5000 (7.8)	
3.0 kg ≤ BW	752 (82.7)	53,392 (83.6)	
Chromosomal abnormality			<.001
Trisomy 21 (Down syndrome)	131 (14.4)	5477 (8.6)	
22q 11 deletion (DiGeorge syndrome)	30 (3.3)	1237 (1.9)	
Trisomy 18 (Edwards syndrome)	12 (1.3)	304 (0.5)	
Other chromosomal abnormality	28 (3.1)	1210 (1.9)	
No chromosomal abnormality	708 (77.9)	55,640 (87.1)	
Early delivery (<37 wk completed gestation)	118 (13.0)	8553 (13.4)	.553
Preoperative mechanical ventilatory support to treat cardiorespiratory failure	76 (8.4)	4973 (7.8)	.521
First-time cardiac surgery (no previous surgery)	608 (66.9)	39,651 (62.1)	.003
Procedure			<.001
VSD repair	113 (12.4)	11,670 (18.3)	
ASD repair	69 (7.6)	6036 (9.5)	
Systemic-pulmonary shunt	48 (5.3)	4328 (6.8)	
PA banding	116 (12.8)	3704 (5.8)	
Fontan	59 (6.5)	3179 (5.0)	
BDG	24 (2.6)	2763 (4.3)	
TOF repair	47 (5.2)	2649 (4.1)	
AVSD repair	26 (2.9)	1634 (2.6)	
Arterial switch operation	13 (1.4)	1324 (2.1)	
DORV repair	10 (1.1)	597 (0.9)	
Other procedures	384 (42.2)	25,984 (40.7)	
CPB use	531 (58.4)	39,679 (62.1)	.010
CPB time (min)	176.9 (±10.3)	139.9 (±1.2)	<.001
Aortic crossclamp time (min)	75.1 (±4.6)	62.2 (±0.5)	<.001
Blood transfusion	704 (77.4)	40,324 (63.1)	<.001
30-d mortality	37 (4.1)	1376 (2.2)	<.001

Results are expressed as the mean (frequency % or ± standard deviation). *PE*, Pericardial effusion; *BW*, body weight; *VSD*, ventricular septal defect; *ASD*, atrial septal defect; *PA*, pulmonary artery; *BDG*, bidirectional Glenn; *TOF*, tetralogy of Fallot; *AVSD*, atrioventricular septal defect; *DORV*, double outlet right ventricle; *CPB*, cardiopulmonary bypass.

time (PE 75.1 vs 62.2 minutes; *P* < .001) were longer, blood transfusions were more frequent (PE 77.4% vs 63.1%; *P* < .001), and 30-day mortality was higher (PE 4.1% vs 2.2%; *P* < .001) in the PE group than in the no PE group.

Multivariable Regression Analysis of the Association With Pericardial Effusion

Multivariable analysis demonstrated that the independent risk factors of postoperative PE were trisomy 21 (OR, 1.54, *P* = .005), 22q.11 deletion (OR, 2.17, *P* < .001), first-time cardiac surgery (OR, 2.01, *P* < .001), and blood transfusion (OR, 1.43, *P* = .007) (Figure 2). On the other hand, factors related to a low risk of postoperative PE were neonatal and infantile age, VSD, ASD, TOF repair, and arterial switch operation. CPB time (OR, 1.0, *P* = .015) and crossclamp time (OR, 1.0, *P* < .001) were demonstrated with neither low nor high risk in multivariable analysis.

DISCUSSION

PE after cardiac surgery is self-limiting and resolves spontaneously in most cases. However, it may manifest unexpectedly as life-threatening cardiac tamponade in others, leading to prolonged hospitalization or readmission. Postoperative PE is known to be an aspect of

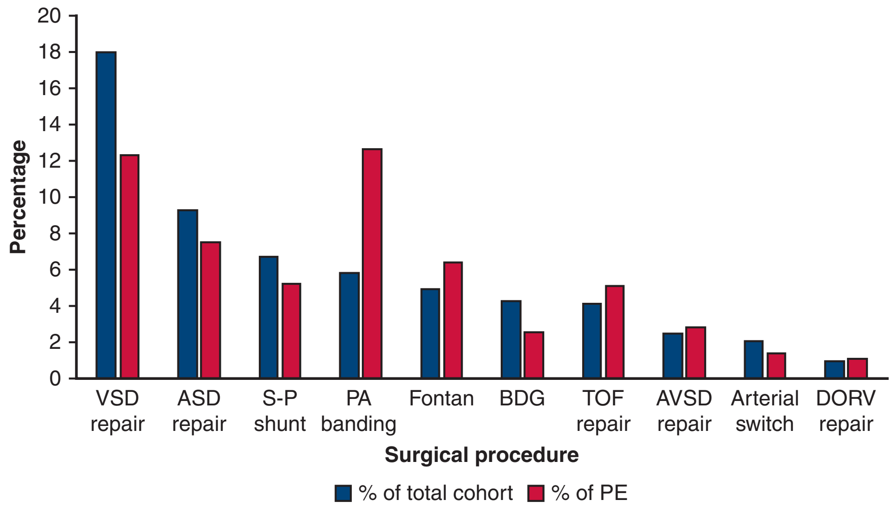

FIGURE 1. Prevalence of surgical procedures and postoperative PE per surgery type. The overall percentage of each surgical procedure (*blue bars*) and the percentage among patients with PE (*red bars*) are shown. *VSD*, Ventricular septal defect; *ASD*, atrial septal defect; *S-P*, systemic-pulmonary; *PA*, pulmonary artery; *BDG*, bidirectional Glenn; *TOF*, tetralogy of Fallot; *AVSD*, atrioventricular septal defect; *DORV*, double outlet right ventricle; *PE*, pericardial effusion.

postpericardiotomy syndrome (PPS), which is currently thought to be an immune-mediated inflammatory process triggered by surgical trauma to the pericardium. From this perspective, aspirin, nonsteroidal anti-inflammatory drugs, corticosteroids, and colchicine are considered effective treatments of postoperative PE because they prevent the immune and autoreactive responses and inflammation.[6-8]

Incidence of Postoperative Pericardial Effusion

Recent reports indicated that postoperative PE has a prevalence of 1.1% to 23% in pediatric or congenital cardiac surgery.[1-4] In the present study, its incidence was low at 1.4% of the total cohort. The cases of postoperative PE in our study were relatively severe, given the inclusion criteria of (1) postoperative PE requiring drainage or (2) PE or tamponade requiring readmission within 30 days after surgery. Most of the mild cases, which were self-limiting or resolved with only medication, were not included in the PE group in the present study.

Age and Gender

Older age was reportedly a risk factor of postoperative PE in cardiac surgery in studies enrolling pediatric patients, whereas younger age was a risk factor in adult studies suggesting that older children and young adults may be more likely to mount an immunologic response and therefore develop severe PE.[1,2,4,6,9-13] Likewise, the risk of postoperative PE was lower in young neonates and infants in the present study. Several studies found that female

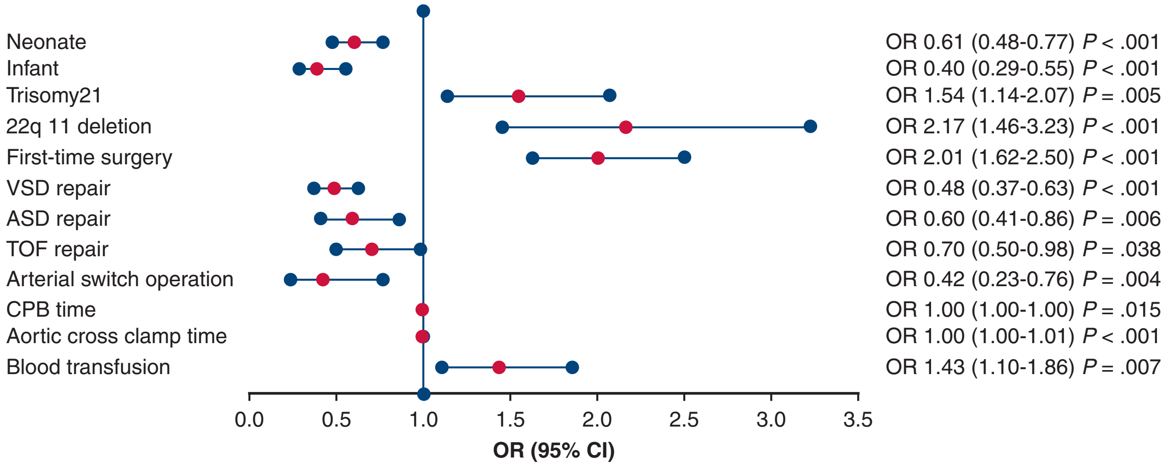

FIGURE 2. Multivariable analysis of PE after congenital cardiovascular surgery. Final multivariable model with OR (95% confidence interval) for each significant variable for comparing patients with and without PE. *VSD*, Ventricular septal defect; *ASD*, atrial septal defect; *TOF*, tetralogy of Fallot; *CPB*, cardiopulmonary bypass; *OR*, odds ratio.

gender was a risk factor of PPS,[4,14] possibly reflecting different predispositions to autoimmune pathogenesis; it is well known that women are more susceptible to a variety of autoimmune disease.[15] However, no difference between genders was evident in our study.

Chromosomal Abnormalities

In recent years, with progress in neonatal and infant care, opportunities for surgical treatment of congenital heart disease in these patients have increased.[16] Michielon and colleagues[17] concluded from their investigation of 787 patients that del 22q11 and trisomy 21 did not represent risk factors of mortality after conotruncal anomaly repair. A study of 45,579 patients in the Society of Thoracic Surgeons Congenital Heart Surgery Database revealed that Down syndrome was not associated with a significant mortality risk in the most common congenital heart operations; however, the postoperative morbidity rate remained high.[18] Down syndrome is associated with a high incidence of PE, which may occur without cardiac surgery and is frequently associated with hypothyroidism, which is also related to PE.[19,20] In our study, trisomy 21 (Down syndrome) and 22q.11 deletion (DiGeorge syndrome) were identified as independent risk factors of postoperative PE on multivariable analysis. This finding was partially corroborated by Elias and colleagues,[2] who demonstrated that trisomy 21, but not 22q.11 deletion, was a risk factor of PE after pediatric cardiac surgery.

First-Time Cardiac Surgery

Our study found first-time cardiac surgery to be an independent risk factor of postoperative PE on multivariable analysis, in line with the findings of Adrichem and colleagues,[1] who demonstrated that previous cardiac surgery was a significant risk reducer. Ashikhmina and colleagues[11] hypothesized that in reoperative patients, the serosal surface is not intact due to pericardial adhesion, thus reducing the pericardial space available for effusions to accumulate than is the case with patients with first-time surgery.

Atrial Septal Defect

Postoperative PE related to surgical repair of ASD has long been studied by researchers. In recent studies, the incidence of PE after ASD repair was 27.5% to 37.1%, with 1.7% to 2.1% of the patients having severe PE requiring drainage.[21,22] Elias and colleagues[2] surmised that an inflammatory reaction secondary to pericardiotomy and right atriotomy combined with chronic volume overload in the right heart may play a role in PE production after surgical ASD repair, although the pathomechanism is still unclear. In the present study, the incidence of relatively severe PE after ASD repair was 1.1% (69/6105 cases), which was similar to that reported by other researchers. However, in the present study, multivariable analysis revealed that ASD repair significantly reduced the risk of relatively severe postoperative PE, suggesting that PE after ASD surgery may be rather less severe or respond well to medication and therefore resolve without drainage. A study examining the age of patients undergoing ASD repair demonstrated that patients older than 5 years had a higher risk of postoperative PE requiring drainage.[23] Thus, it may be inferred that the reason for the frequency of postoperative PE after ASD repair may be the relatively older age of the patients than in other types of congenital heart surgery rather than the ASD repair itself. Moreover, most of the patients with PE in the study cited were receiving surgery for the first time, which the present study revealed to be an independent risk factor of postoperative PE. Because of the increasing rate of transcatheter closure of secundum ASD in recent years, surgical closure of an ASD tends to be used less often in young patients with heart failure.[24] If this trend continues, the incidence of postoperative PE after ASD repair may decrease in the future.

Surgical Procedures

No surgical procedure was identified as a risk factor of postoperative PE in the present study. On the other hand, VSD repair, TOF repair, arterial switch operation, and ASD repair were found to be associated with a low risk on multivariable analysis. In congenital heart surgery, various high- and low-risk procedures for postoperative PE have been reported, but the findings are sometimes contradictory for reasons that are still unclear. Some studies have reported VSD repair and arterial switch operation as low-risk procedures, in line with our own findings.[2-4]

Pulmonary Artery Banding

Among the various surgical techniques examined in the present study, PA banding was most often associated with PE (12.8%) despite the results of multivariable analysis indicating the absence of any such association. PA banding, commonly performed in Japan, is a less-invasive, palliative procedure that does not use CPB and controls pulmonary overflow in critically ill patients. A previous study using a canine PA banding model revealed that acute afterload-induced right ventricle failure from PA banding was associated with increased myocardial expression of inflammatory cytokines and neutrophil and macrophage infiltration,[25] creating conditions favorable for the development of PE. Moreover, many patients undergoing PA banding have Down syndrome, which was found to be an independent risk factor of postoperative PE, thus making postoperative PE more common in patients receiving PA banding.[26]

Cardiopulmonary Bypass

Previous studies reported prolonged CPB duration and longer aortic crossclamp time as risk factors of postoperative PE.[9,11] CPB is known to initiate a systemic inflammatory response that can contribute to PPS development, and this inflammatory response may be aggravated by the presence of blood in the pericardial space. CPB and aorta crossclamping also induce myocardial hypoxia and ischemia, both of which are proinflammatory stimuli.[1,27] However, in the present study, CPB time and aortic crossclamp time were demonstrated with neither low nor high risk (OR, 1.0) in multivariable analysis. The lower frequency of CPB use in the PE group in univariable analysis might have been influenced by PA banding in the no PE group. No significant difference in the association with CPB use between the groups was detected by multivariable analysis.

Blood Transfusion

The present study found that blood transfusions were frequently performed in patients with postoperative PE and that it was an independent risk factor of PE development. These findings were supported by a report of an association of bleeding and red blood cell use with PPS occurrence.[28] Surgical trauma and intraoperative effusion were suggested as potential stimuli for PPS development; however, the causality has not been established.

Mortality

Although most cases of postoperative PE or PPS are reportedly associated with increased morbidity, longer postoperative hospitalization, and more frequent readmission, most patients have a benign clinical course with a good overall prognosis and low risk of mortality.[14,15] Lehto and colleagues[12] reported that PPS development was associated with higher mortality within the first year after cardiac or ascending aortic surgery in their study of adult patients. In the present study, the 30-day mortality rate was unexpectedly high at 4.1% in patients with postoperative PE. Although the reasons are still unclear, these findings strongly underscore the need to pay close attention to the clinical course of patients with relatively severe postoperative PE.

Study Limitations

This study has several limitations due to its retrospective nature. First, as mentioned earlier, relatively severe cases of postoperative PE were investigated; the inclusion of mild cases may have produced different results. Second, because the variables investigated were limited by the data available in the JCCVSD, there might have been other factors affecting the outcomes. For example, information on perioperative fluid management and laboratory tests was unavailable. Also, preoperative and postoperative medications were not considered despite the possibility that they may have affected the risk of postoperative PE. Nonetheless, the present study was based on a nationwide registry covering almost all the hospitals in Japan, and analytical reports from the database are considered to be highly representative of routine clinical care in Japan.

CONCLUSIONS

We described the risk factors of PE after congenital heart surgery by analyzing data from a multi-institutional

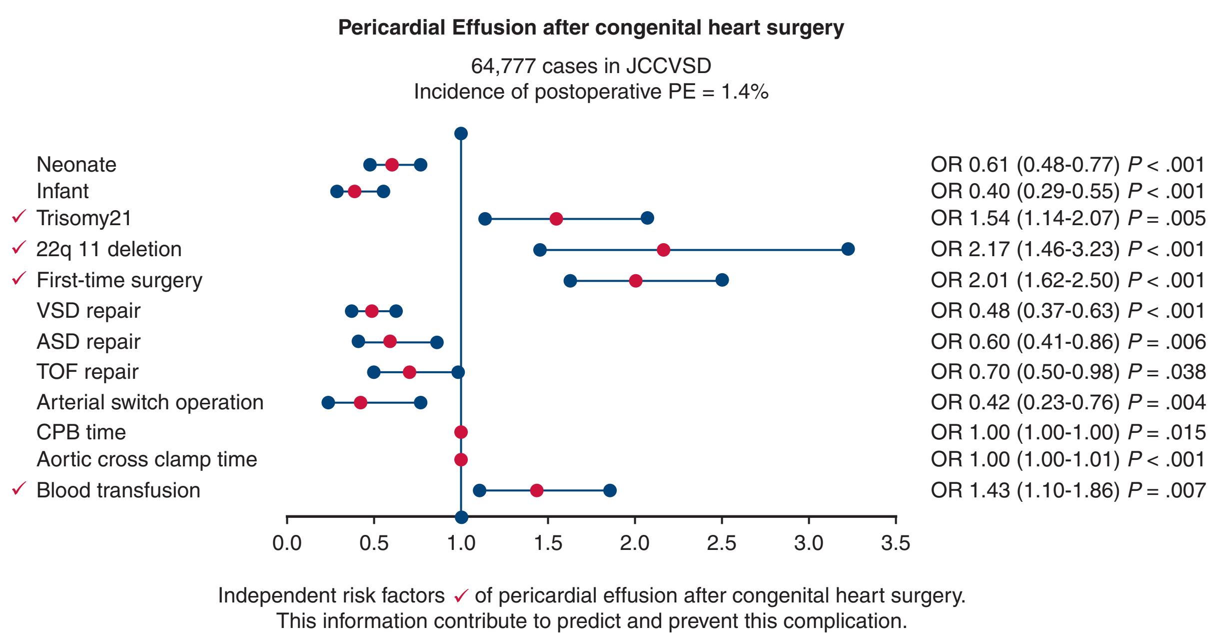

FIGURE 3. Graphical summary of the study. *JCCVSD*, Japan Congenital Cardiovascular Surgery Database; *PE*, pericardial effusion; *VSD*, ventricular septal defect; *ASD*, atrial septal defect; *TOF*, tetralogy of Fallot; *CPB*, cardiopulmonary bypass.

database that reflects routine clinical care in Japan. The incidence of postoperative PE in pediatric or congenital cardiac surgery was 1.4% in the total cohort. The independent risk factors of postoperative PE on multivariable analysis were trisomy 21, 22q.11 deletion, first-time cardiac surgery, and blood transfusion (Figure 3). These factors may enable physicians to predict the need for drainage of postcongenital heart surgery PE. In contrast, neonates, infants, VSD, ASD, TOF repair, and arterial switch operation were related to a low risk of PE development.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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