Original Article

Outcome of Late Extracardiac Fontan Completion in Functional Single Ventricle Patients

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Objective: To determine the clinical outcomes and factors influencing the results of late Fontan completion in functional single ventricle patients.

Material and Methods: The authors retrospectively analyzed data in functional single ventricle patients that underwent late Fontan completion (age more than four-year-old) between January 2007 and December 2017.

Results: The extracardiac conduit Fontan procedure was performed in thirty-six patients over four years old (median age 10 years). The early mortality rate was 11% and the overall mortality was 16%. According to the Cox regression analysis, pulmonary artery pressure greater than 15 mmHg was an unfavorable factor for hospital death. Other morbidities included persistent pleural effusion (44%), chylothorax (2.78%), early atrial tachycardia (5.56%), early graft thrombosis (5.56%), and late graft thrombosis (2.78%).

Conclusion: Late extracardiac conduit Fontan completion yielded acceptable outcomes. The authors found pulmonary artery pressure greater than 15 mmHg to be a risk factor for early mortality. Prevalence of postoperative persistent pleural effusion was higher in older patients, while rates of other complications did not differ from other age groups.

Keywords: Fontan operation, Late Fontan operation, Single ventricle, Functional single ventricle, Univentricular heart

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The Fontan operation is considered the definitive palliative procedure for the treatment of patients with univentricular heart physiology. The Fontan operation was first performed in 1971 by Dr. Francois Marie Fontan for the treatment of tricuspid atresia. Since then, the classical Fontan procedure has been modified to several techniques. Extracardiac conduit (ECC) Fontan is currently the preferred procedure, as it results in fewer long-term complications when comparing to the atriopulmonary connection and lateral tunnel techniques[1].

Recent improvements in surgical technique and post-operative care have resulted in reduction of the mortality and post-operative complications of Fontan procedure. However, the long-term complications that occur following the Fontan procedure remain a concern. As Dr. Fontan mentioned, this operation did not resolve the anatomical problem, it only corrected the physiology. Thus, it is impossible to avoid complications after this surgery. There are many factors that play a role in determining the surgical outcomes. One is the age of the patient at the time of Fontan completion, which is still dubious. Currently, most surgeons prefer to perform the operation when the patient is around 2 to 4 years of age, as many studies have supported the benefits of performing the operation in younger patients. These include a reduction in the risk of post-operative mortality and morbidity[2] and improvements of quality of life with regard to exercise capacity[3]. However, some studies have reported no significant difference with regard to either mid-term or long-term surgical outcomes when Fontan completion is performed in older patients[4,5]. The optimal age at which Fontan completion should

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be performed, thus, remains inconclusive.

Objective

The aim of the present study was to focus on the patients with a functional single ventricle that underwent ECC Fontan at a late age defined as age more than 4-year-old, and to review the outcomes of the surgery in terms of mortality rates, post-operative complications, and factors affecting the results.

Materials and Methods

The present study was performed at Srinagarind Hospital and Queen Sirikit Heart Center of the Northeast at Khon Kaen University's Faculty of Medicine and approved by the Ethical Board of the University.

The medical records of patients who were more than four years old and underwent the ECC Fontan operation between January 2007 and December 2017 were retrospectively reviewed. Demographic, laboratory, non-invasive imaging, cardiac catheterization, pre- and peri-operative, post-operative complication, hospital stay, and follow-up data were collected. Patient characteristics are shown in Table 1.

Table 1. Patient characteristics (n = 36)

Variables	n (%)
Age at ECC (years), Median (range)	10 (5 to 24)
Weight at ECC (years), Median (range)	27.6 (12 to 60)
Height at ECC (years), Median (range)	135 (96.5 to 165)
Sex: male	19 (52.78)
Primary diagnosis	
TA with IVS	7 (19.44)
TA with VSD	7 (19.44)
DORV	8 (22.22)
PA with IVS	1 (2.78)
Unbalanced AVSD	1 (2.78)
Heterotaxy syndrome	12 (33.33)
Dominant RV	5 (13.89)
Dominant LV	31 (86.11)

ECC=extracardiac conduit Fontan; TA=tricuspid atresia; IVS=intact ventricular septum; VSD=ventricular septal defect; DORV=double outlet right ventricle; PA=pulmonary atresia; AVSD=atrioventricular septal defect; RV=right ventricle; LV=left ventricle

Preoperative catheterization was performed in every case. Crucial parameters, such as pulmonary artery (PA) pressure, were measured. The anatomy of the heart, ventricular function, PA size, and configuration were evaluated.

Operative technique

ECC Fontan was performed via median sternotomy and on cardiopulmonary bypass with aortic and bicaval cannulation without an aortic cross-clamp, except in case requiring concomitant valve surgery, aortic cross clamp would be applied. The previous superior cavopulmonary shunt and PA were dissected to enable full exposure. The inferior vena cava (IVC) was dissected down to the diaphragmatic surface before a cannula was inserted. A polytetrafluoroethylene graft (Goretex) was used. The size of the conduit grafts varied from 16 to 22 mm depending on the patient's weight and IVC size. The operation was performed under mild hypothermic conditions. The IVC was separated from the heart and connected to the tube graft. The proximal of the tube graft was sutured to the inferior portion of the central PA opposite the superior cavopulmonary shunt and slightly extended to the left side. In cases of concomitant PA stenosis, PA plasty would be performed at the same time. When indicated, a 4 mm fenestration was created using a punch and connected between the right atrium and tube graft.

Follow-up data

The pediatric cardiologist and cardiac surgeons in outpatient unit followed up all patients. Mortality and post-operative complications were regularly monitored. Routine physical examination, electrocardiography, and chest X-ray were performed at each visit. The first session of outpatient echocardiography was performed by a pediatric cardiologist at two weeks after discharge. Further investigation such as cardiac catheterization, cardiac magnetic resonance imaging (MRI), abdominal ultrasound with liver function test were performed as clinically indicated.

Definitions

Late Fontan completion was defined when Fontan operation was performed in patient who were older than four-year-old.

Early or hospital mortality was defined as death occurring within 30 days after surgery. Overall mortality included both early and late mortality.

Post-operative complications included early and delayed complications. Early complications were defined as any complications occurring within 30 days after the procedure. Delayed complications were

defined as any complication occurring after 30 days post operation.

Prolonged pleural effusion drainage was defined as continuous pleural drainage for more than 14 days following the operation.

Statistical analysis

Continuous variables were presented as means with standard deviation or median with range. Categorical variables were presented as numbers or percentages. The student t-test was used for normally distributed variables and the Mann-Whitney test was used for non-normal distribution. Both were applied to compare continuous variables. Chi-square tests and Fisher's exact tests were used for the comparison of categorical variables. The cox regression model was used to evaluate the association between risk factors and hospital mortality. A p-value smaller than 0.05 was considered significant. Statistical analyses were performed by using Stata version 13.0 (StataCorp, TX).

Results

Baseline patient characteristics

Thirty-six patients, older than four years of age, underwent the ECC Fontan operation between 2007 and 2017 and were included in our study. The median follow-up period was five years (range 1 to 8 years). The median age was 10 years. The youngest patient was five years old. The oldest was 24 years old. Nineteen of the patients were male (52.78%), and the median weight at surgery was 27.6 kg. Most patients were diagnosed with tricuspid atresia (38.88%), and most were left ventricular dominant (86.11%). Patient characteristics are shown in Table 1.

About 60% of the patient presented with inadequate pulmonary blood flow and required a palliative procedure such as a modified Blalock Taussig shunt or central shunt. One patient presented with congestive heart failure and required PA banding during the neonatal period. All patients underwent a bidirectional Glenn shunt (BDG) as second-stage palliation at a mean age of five years (four months to 21 years). The median time interval from BDG to Fontan completion was three years (one to 10 years). The median age at the time the patient underwent the Fontan procedure was 10 years. Half of the patients underwent the Fontan operation when they were over 10 years old. Most patients had pre-operative PA pressure of less than 15 mmHg (Table 2).

All patients underwent ECC Fontan. The median CPB time was 144 minutes. Two patients required atrioventricular valve repair as a concomitant procedure due to valve insufficiency, which required aortic cross clamping. PA plasty was performed in one patient who had proximal left PA stenosis. One patient required atrial septectomy to correct atrial septal restriction. Nineteen patients (52.78%) required fenestration as clinically indicated such as PA pressure greater than 15 mmHg, unfavorable PA configuration, concomitant PA reconstruction, had previously presented with chylothorax, or suffered from prolonged pleural effusion at the time the Bidirectional Glenn operation was performed. The 4-mm fenestration was made at graft and sutured directly to the right atrium at which a small incision had been made, which was controlled with a partial clamp. Graft sizes varied between 16 to 22 mm. The graft used was 16 mm in five patients (13.89%), 18

Table 2. Preoperative data

Variables	n (%)
Initial palliation	
Blalock-Taussig shunt	20 (55.56)
Central shunt	2 (5.56)
PA banding	1 (2.78)
Prior staging procedure	
BDG	36 (100)
Age at Fontan procedure (years)	
Age >4 to 10	18 (50.00)
Age >10	18 (50.00)
PA pressure (mmHg)	
<15	31 (80.56)
≥15	5 (13.89)

PA=pulmonary artery; BDG=bidirectional Glenn shunt

Table 3. Perioperative data

Variables	n (%)
CPB time (minute), Median (range)	144 (73 to 303)
Concomitant procedure	
AVV repair	2 (5.56)
PA reconstruction	1 (2.78)
Atrial septectomy	1 (2.78)
Fenestration	19 (52.78)
Graft size (mm), Median (range)	18 (16 to 22)

CPB=cardiopulmonary bypass; AVV=atrioventricular valve; PA=pulmonary artery

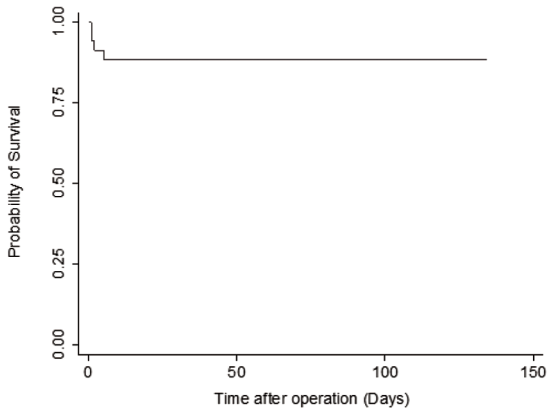

Figure 1. Kaplan-Meier estimated of early survival of the patients following extracardiac Fontan completion, 95% CI 72.36% to 95.55%.

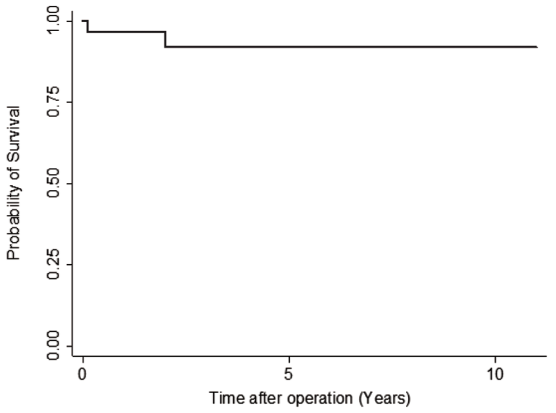

Figure 2. Kaplan-Meier estimated of late survival of the patients following extracardiac Fontan completion, 95% CI 70.83 to 98.02%.

mm in 11 (30.56%) patients, 20 mm in 11 (30.56%) patients, and 22 mm in nine (25%) patients (Table 3).

Post-operative mortality

Four patients died within 30 days after the surgery, three died from low cardiac output and ventricular failure, and one died from massive bleeding that required re-operation, complicated by multi-organ failure. There was an 88.89% early (first 30 days) survival rate (Figure 1). There were two late mortalities with a median time follow-up duration of five years. The overall five-year survival rate was 83.33% (95% CI 70.83 to 98.02%), as shown in Figure 2. One patient died two months after the operation from severe sepsis, another died two years later due to cardiac cirrhosis and multi-organ failure after graft revision.

Table 4. Mortality rate and postoperative morbidities

Variables	n (%)
Early mortality	4 (11.11)
Late mortality	2 (6.25)
Prolonged pleural effusion drainage (days)	16 (44.44)
Mean (range)	17 (2 to 61)
Chylothorax	1 (2.78)
Arrhythmia	2 (5.56)
Thrombosis	3 (8.33)

Post-operative morbidity

Two patients required re-operation in the early post-operative period due to bleeding. Sixteen patients had prolonged pleural effusion drainage (of more than 14 days) and required chest tube retaining (mean 17 days). One patient developed chylothorax, which improved with conservative treatment. Two patients developed transient tachyarrhythmia in the early post-operative period and required antiarrhythmic control.

Late graft thrombosis was found in three patients (8.33%) (Table 4). Two developed partial thrombosis in the first year after surgery and were treated successfully with anticoagulants, while the other had a problem with graft kinking and required re-operation for correction. This latter patient ended up with cardiac cirrhosis and multi-organ failure two years after the initial Fontan operation. There were no other late complications, such as arrhythmia, protein losing enteropathy, plastic bronchitis, or Fontan failure, observed in the present study. Seventy-five percent of the patients required admission for more than two weeks due to persistent pleural effusions.

Risk factors for increased mortality rate

Risk factors for hospital mortality within the first 30 days are shown in Table 5. Pulmonary pressure of more than 15 mmHg was the only factor that was related to early death.

Discussion

Early and late mortality

The authors' institution began performing ECC Fontan procedures in 2004. Since then, surgical outcomes have improved, and mortality has decreased. Chikitpingyo et al[6] retrospectively reviewed the mortality rate after the Fontan procedure in all age group patients in the present institution and found

Table 5. Hazard ratios for risk of hospital mortality outcome

Variables	HR	95% CI	p-value
Sex: male	2.72	0.28 to 26.13	0.355
Age (years)	1.14	0.16 to 8.11	0.895
Dominant RV	5.16	0.73 to 36.64	0.119
Heterotaxy	6.49	0.67 to 62.61	0.075
Fenestration	2.00	0.21 to 19.23	0.528
PA pressure ≥15 mmHg	11.07	1.15 to 106.64	0.022
CPB time ≥120 minutes	1.55	0.16 to 14.91	0.695

RV=right ventricle; PA=pulmonary artery; CPB=cardio-pulmonary bypass; HR=hazard ratio; CI=confidence interval

that the early mortality rate about was 11%, which is comparable to that found in the authors' study. Other studies had also reported early mortality rates of between 5% to 13%[7]. Prachasilchai et al[8] reported the early mortality rate to be about 18% in older patients (mean age 7.4 years). The overall mortality rate in the present study was 16%. The main cause of early death was low cardiac output as a consequence of ventricular failure. The authors found pulmonary pressure greater than 15 mmHg to be a significant risk factor for early mortality (within 30 days). This is consistent with the results of previous studies, which found that PA pressure greater than 15 mmHg can lead to unfavorable outcomes[9,10]. However, the other potential risk factors, such as age older than 10 years, cardiopulmonary bypass time, heterotaxy syndrome, dominant ventricle, or fenestrate creation, did not affect the outcome. Other common unfavorable factors that have been reported were not identified in the present study, included presenting of common atrioventricular valve[9,11,12], prolonged deep hypothermic circulatory arrest, and impaired ventricular function[10]. As there were few patients in the present study that suffered from late mortality, the authors did not analyze the associated risk factors. Schwartz et al[13] conducted a meta-analysis of 5,859 patients and found the significant factors associated with late death were the type of Fontan procedure and older age at the time of Fontan. Other factors reported were heterotaxy syndrome, moderate to severe atrioventricular valve regurgitation, prolonged cardiopulmonary bypass time, and prolonged aortic cross-clamp[14]. Alsaied et al[15] reviewed the records of 6,707 patients, found the most common cause of late death to be heart/Fontan failure (22%), arrhythmia (16%), respiratory failure (15%), renal disease (12%), and thrombosis/bleeding (10%).

Age at the time of Fontan operation

Currently, there is no consensus regarding the optimal age for Fontan completion. In the institute, the authors prefer to perform the modified Fontan operation when the patient is around two to four years of age. However, there are some patients who seek treatment late or do not follow-up, especially after having undergone the staged procedure. Because of these, almost 25% of the patients receive Fontan completion when they are over four years old. Although, there is no exact optimal age to undergo the Fontan operation, most surgeons tend to perform the operation early due to early unloading ventricle, less atrioventricular valve regurgitation, better exercised activity, and improved long-term outcome and survival rate. Performing the operation early has also been shown to result in fewer post-operative complications such as arrhythmia[16-18] and pleural effusion[19]. Recently, there was a report published that found that the Fontan procedure yielded acceptable surgical outcomes in infants[20]. In addition, another study found that the surgery could be performed in pediatric patients who weighed less than 10 kg[18].

However, some surgeons prefer to delay surgery to allow the patient to grow enough to be fit with larger grafts[4]. Other studies have reported no difference in the mortality rates of adult and pediatric patients[1,4,21]. Deraz et al[22] reported that age had no influence on the outcomes or ventricular function. This suggests that further study or systematic review about the optimal age the patients should undergo the Fontan procedure may be required.

Fenestration

Fenestrated Fontan was first described by Bridges et al (1990). It is indicated in high-risk patients to diminish post-operative complications such as low post-operative cardiac output, pleural and pericardial effusion, ventricular dysfunction, exercise intolerance, and protein-losing enteropathy[23]. Fenestrated Fontan is performed routinely at some institutions. However, some studies showed no difference in terms of late outcomes between patients that underwent the fenestrated Fontan procedure and those that underwent the non-fenestrated procedure[24]. In addition, fenestration can cause complications, such as systemic emboli, stroke, decreased exercise tolerance, and systemic desaturation[24,25], which were not found in the authors' study. Therefore, it is recommended that fenestration only be performed in selective

cases. The authors also have the selective criteria for fenestration in patients who are at risk for Fontan failure including those with PA pressure greater than 15 mmHg, unfavorable PA configuration, concomitant PA reconstruction, have previously presented with chylothorax, or suffered from prolonged pleural effusion at the time the bidirectional Glenn operation was performed. In the present study, the authors found that majority of patients had PA pressure greater than 12 mmHg. The mean PA pressure of patients with mortal outcomes was more than 15. About 50% of the present patients received fenestration at the time of Fontan completion.

Prolonged pleural effusion drainage, chylothorax, and protein losing enteropathy

Prolonged effusion is a common problem after undergoing the modified Fontan procedure especially in cases in which ECC Fontan is performed[26]. In the present series, 44% of patients developed prolonged pleural effusion and one patient developed chylothorax. This number is quite high when compared to other studies, in which the incidence of post-operative persistent pleural effusion was about 37% to 38.9%[27,28]. Vogel et al[19] reported that patients younger than 2.5 years old had less prolonged pleural effusion when compared to older patients, which is consistent with a study by Fedderly et al[29] that found the patients over four years of age had significantly higher rates post-operative persistent pleural effusion. Although the risks factors that contribute to prolonged pleural effusion are unclear, pre- and post-operative infection, non-fenestration, and low pre-operative oxygen saturation may be related[27,29]. Prolonged pleural effusions after the Fontan procedure is a challenging problem and can lead to increased post-operative morbidity and prolonged hospital stay. Poh et al[11] reported that prolonged pleural effusion is a significant predictor of late death post-Fontan surgery (HR 1.18, 95% CI 1.09 to 1.29, $p<0.001$). Some protocols have been developed to decrease the risk of this complication occurring such as the early initiation of diuretic, fluid restriction, continued oxygen supplementation, and a low-fat diet[30]. This protocol is similar to the techniques the authors used in the management of patients with persistent pleural effusion. Fortunately, all of the present patients who developed persistent pleural effusion and chylothorax improved with conservative treatment and no further procedures were required. Protein losing enteropathy is also one of the common complications after Fontan procedure. Most patients have gastrointestinal symptoms such as diarrhea, abdominal pain, hypoalbuminemia, hypoproteinemia, low serum calcium, lymphocytopenia, elevated alpha-1 antitrypsin in the stool and increased alpha-1 antitrypsin clearance. Technetium 99m-labeled human serum albumin scintigraphy may be used to confirm the diagnosis. In the authors institute, the physicians usually consider the patients developing protein losing enteropathy complication when they present with gastrointestinal symptoms and blood tests show characteristic of protein losing as previously mentioned. There were no cases of protein-losing enteropathy following the procedure in the present study.

Graft thrombosis

The incidence of post-operative Fontan thrombosis and thromboembolic events varies from 3% to 20%[31]. The risk factors for this condition include chronic systemic venous hypertension, protein losing enteropathy, passive blood flow, conduit stenosis, prosthetic material used, prolonged using of central venous lines, and lower FiO_2 after the procedure[31,32]. Three patients developed graft thrombosis in the present study (8.3%). Two were diagnosed with early partial thrombosis and treated successfully with anticoagulant before discharge. One patient had the problem with graft kinking from the surgical technique and required re-operation for correction. Early administration of low molecular weight heparin (enoxaparin) and warfarin were initiated post-operatively to prevent graft thrombosis according to the present protocol. When the international normalized ratio (INR) is in therapeutic level as 1.5 to 2, administration of Enoxaparin is discontinued while warfarin is continued for two years after the surgery. Some institutions may prefer to use aspirin as a prophylactic medication instead of warfarin. Some studies found no difference in terms of effectiveness between aspirin and warfarin in cases of thrombotic prophylaxis[32,33]. However, care should be taken in administering aspirin in adult patients, as aspirin resistance can occur due to increased platelet activities[34].

Arrhythmia

Atrial tachyarrhythmia is a major late complication in adult Fontan patients. Giannakoulas et al[2] reported that late atrial tachyarrhythmia in adult patients is associated with higher morbidity and mortality at a mid-term follow-up. However, early arrhythmia did not affect the outcome. The prevalence of overall atrial

arrhythmia following ECC Fontan is approximately 8% to 15%[24,35,36]. The occurrence rate of early tachyarrhythmia post-operation has been shown to be about 8%[35], which is comparable to the present results. In the present study, two patients (5%) developed early tachyarrhythmia and were treated successfully with medication. Recent studies have reported that the prevalence of clinically relevant arrhythmia increases significantly with age[37,38]. However, the authors did not find any relationship between age and arrhythmia in the present study. No late arrhythmia was observed at a five-year follow-up. The risk factors for post-operative arrhythmia are still unclear. Atriopulmonary connection or lateral tunnel modified Fontan operations are particularly likely to be risk factors for post-operative arrhythmia[36]. However, in a report by Balaji et al[35], the type of Fontan was not related to arrhythmia outcome. Other risk factors to increase post-operative arrhythmia include heterotaxia syndrome and common atrioventricular valve[11].

Hepatic dysfunction

The Fontan operation is associated with late hepatic dysfunction due to systemic venous congestion. A report by Agnoletti et al[39] found that cardiac output had decreased significantly five years after the operation, while New York Heart Association (NYHA) class had increased significantly. Patients with NYHA class II/III have been shown to have remarkably higher hepatic pressure levels. In the authors' institution, a hepatic function test is conducted once early in the follow-up period and subsequently as clinically indicated. There is no policy to perform routine abdominal ultrasounds except in cases that clinical or lab data are abnormal. However, recent studies have reported that lab abnormality detection is probably not sensitive enough to detect hepatic problems early as most patients who have Fontan-associated liver disease (FALD) are asymptomatic and have normal hepatic function[24,40]. This may be the reason the authors could not identify any patients who had late FALD following the procedure. High-frequency ultrasound transducer is a good screening tool for early FALD detection and may also be able to detect early-stage fibrosis by demonstrating hyper-echoic lesions without surface nodularity[41].

Limitation

The limitation of the present study is that it was retrospective and conducted in a single institute. There was also limited data on late mortality and morbidity due to the short follow-up period. The small number of patients might also limit the reliability of the present study in terms of statistical analysis and the identification of risk factors.

Conclusion

The authors found that late ECC Fontan completion yielded acceptable outcomes. The mortality rate was comparable to that in younger patients. The main causes of death were the ventricular failure and low cardiac output. High PA pressure (greater than 15 mmHg) was found to be a risk factor for early mortality. The prevalence of post-operative persistent pleural effusion was higher in older patients following the procedure, but the other complications, such as PLE, arrhythmia, graft thrombosis, and hepatic dysfunction, did not differ from the other patients.

What is already known on this topic?

Although most surgeons prefer to perform early Fontan operation, the optimal age at the time of Fontan completion is still a controversy. This is because the outcomes of the patient that underwent late Fontan operation remain inconclusive.

What this study adds?

The outcomes of late Fontan completion are acceptable and comparable to early completion. However, the incidence of post-operative persistent pleural effusion is higher.

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Conflicts of interest

The authors declare no conflict of interest.

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