Predictors of Prolonged Mechanical Ventilation in Paediatric Patients After Anatomical Correction of Simple Congenital Heart Disease

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Visual abstract

Key question: Predict the risk of prolonged mechanical ventilation (>24 h) before surgery.

Key findings: Preoperative prediction of postoperative prolonged mechanical ventilation (>24 h) risk is reliable.

Take-home message: The prediction model of risk of prolonged mechanical ventilation (>24 h) after surgery is constructed with good accuracy.

Abstract

Background:

We aimed to use preoperative clinical data from paediatric patients with simple congenital heart disease to predict the risk of prolonged mechanical ventilation after surgery.

Methods:

The clinical data from paediatric patients with simple congenital heart disease who underwent anatomical correction under cardiopulmonary bypass in a single centre during a continuous period were retrospectively collected. Univariate and multivariate logistic regression analyses were performed to identify the risk factors for prolonged mechanical ventilation (>24 h) after surgery, and a mathematical model was established. Then, using data from another centre, we adopted an ROC curve to verify the scalability of the model.

Results:

A total of 585 paediatric patients were eligible for inclusion in this study. Multivariate logistic regression analysis showed that weight (kg), the size of the ventricular septal defect, the size of the atrial septal defect and the shunt direction of the defect site were significantly correlated with prolonged mechanical ventilation (>24 h) after surgery. The risk prediction model was established and the area under the curve of the model was 0.853 (ROC curve). A set of data from another heart centre, with equivalent inclusion criteria, was used to validate the scalability of the model, and the area under the curve of the accepted validated data was 0.841 (ROC curve).

Conclusions:

The risk of prolonged mechanical ventilation (>24 h) after surgery in paediatric patients with simple congenital heart disease with anatomical correction assisted by cardiopulmonary bypass can be well predicted by using preoperative clinical data.

Keywords: Congenital Heart Disease; Mechanical Ventilation; Surgery; Cardiopulmonary Bypass; complications

Article word： 2788 words.

1 Introduction

The incidence of congenital heart disease (CHD) is approximately 3-6 in 1,000, and CHD is one of the main causes of birth malformations and deaths in newborns [1,2]; more than 60% of cases are simple CHDs[2], such as atrial septal defects (ASDs), ventricular septal defects (VSDs), and a patent ductus arteriosus (PDA), which may exist alone or in combination [3]. This group of paediatric patients is defined as having simple CHD because it is known at the time of diagnosis that they can undergo anatomical correction. The development of transcatheter closure technology has enabled some simple CHD patients to avoid thoracotomy repair, and most paediatric patients who receive transcatheter closure can recover quickly after surgery, but transcatheter closure is not applicable to all simple CHD paediatric patients[4,5]. Most paediatric patients with simple CHD who receive cardiopulmonary bypass (CBP)-assisted anatomical correction surgery can obtain a good prognosis[5], and the greatest problem for such paediatric patients is perioperative safety. Prolonged mechanical ventilation (PMV) after surgery is a cause and effect of many other complications, so how to avoid or predict PMV after surgery is particularly important[6]. This study retrospectively collected data from paediatric patients with CHD who received CBP-assisted anatomical correction in an experienced heart centre.

Combined with the results of previous studies[7,8], the preoperatively available data were used to evaluate the risk factors for PMV in these paediatric patients and to establish a prediction model. We hope that the possible risk factors can be perceived and improved in advance, and perioperative risk can be reduced.

2 Materials

This study collected data from paediatric patients (age: 7 d to 14 years) with simple CHD who received anatomical correction under CBP in a single centre from 2012 to 2019. These data include ASD, VSD, PDA, right ventricular outflow tract stenosis, pulmonary hypertension, etc. We excluded some complex CHD cases, including all patients in whom anatomical correction could not be identified preoperatively, such as those with tetralogy of Fallot, a single atrium or single ventricle, defects with right to left shunting, and endocardial cushion defects. In addition, in order to have better comparability of data, we excluded premature babies and children with obvious extracardiac deformities. Data from paediatric patients with interventional closure therapy were excluded. Finally, 585 children were eligible for the study (figure 1). Ninety-three paediatric patients needed mechanical ventilation for more than 24 hours after surgery. Of these, 20 had respiratory problems, and 73 had unstable circulation. The clinical data collected included age, sex, weight, preoperative routine blood test results, preoperative colour Doppler ultrasound information, etc. (table 1). Furthermore, we collected clinical data from 164 paediatric patients with the same inclusion criteria from another heart centre from 2018 to 2019 to verify the model.

The timing of postoperative extubation was jointly decided by anesthesiologist, cardiac surgery care unit doctor, and surgeon.The main criteria for stopping mechanical ventilation: 1)Blood pressure of children with discontinuation or low-dose use of inotropic drugs can be

maintained within the normal range, 2)Arterial blood gas analysis indicates oxygenation index≥300, 3)Positive End Expiratory Pressure(PEEP) < 10, 4)Use Preassure Support Ventilation(PSV) mode or Synchronized Intermittent Mandatory Ventilation(SIMV) mode as transitional ventilation mode before tracheal intubation removed,with spontaneous breathing and spontaneous tidal volume≥5ml/Kg during transitional ventilation mode.

All paediatric patients included in this study achieved anatomical correction, and echocardiography was re-examined before discharge. In 17 cases, a small amount of residual shunting was observed at the repair site of the ventricular septal defect, but all of them were less than 2 mm, and the ejection distance was less than 1.5 m, which was considered to be unnecessary[9]. Table 1 shows that 2 children in the PMV group died.One of the children suffered severe pulmonary infection and died after PMV (114h) after surgery, and the other died of heart failure after 79 hours of mechanical ventilation.

In addition, it is worth noting that in our data, there are 63 cases with bidirectional shunt at the defect site.This bidirectional shunt that still exists after strict medical treatment, including oral bosentan or viagra. Among them, 47 cases are mainly left to right shunt, and 16 cases are right to left shunt.All patients underwent right heart catheterization before operation, which indicated that pulmonary vascular resistance less than 5wood or oxygen inhalation for 10-15 minutes could reduce pulmonary artery pressure by 20-30%.Therefore, preoperative evaluation suggested that anatomical correction could be performed in these children.

3 Statistical method

Univariate and multivariate regression was used to analyse the relationship between patient age, sex, weight, preoperative cardiac ultrasound and postoperative PMV and to establish a logistic regression model. ROC curves were used to verify the consistency between the regression model and the occurrence of PMV. The extensibility of the prediction model was verified by using external data. SPSS20.0 software was used for the statistical analysis described above. Finally, R language was used to draw nomogram to visualize the prediction model and draw calibration curves to varify the prediction model.

4 Results:

4.1 Risk factors associated with postoperative PMV

A total of 585 paediatric patients were eligible and eventually included in this study, including 93 patients with postoperative PMV. Univariate regression confirmed that age (OR: 0.67, 95% CI: 0.58-0.78, P<0.001), height (OR: 0.95, 95% CI: 0.93-0.96, P<0.001), weight (OR: 0.75, 95% CI: 0.70-0.81, P<0.001), size of the ASD (OR: 0.96, 95% CI: 0.93-1.0, P=0.045), size of the VSD (OR: 1.14, 95% CI: 1.09-1.20, P<0.001), pulmonary hypertension (PH) (OR: 2.03, 95% CI: 1.68-2.45, P<0.001), diameter of the main pulmonary artery (MPA) (OR: 0.90, 95% CI: 0.85-0.96, P=0.001), diagnosis (OR: 1.32, 95% CI: 1.17-1.50, P<0.001), and shunt direction of the defect site (OR: 8.47, 95% CI: 4.82-14.87, P<0.001) were associated with the incidence of postoperative PMV. Ultimately, we included nine factors, including weight, into the multivariate regression model, considering the correlation between all factors and the limitation of sample size. The results are shown in table 2.

4.2 Multivariate logistic regression was used to establish a prediction model

Multivariate logistic regression analysis showed that the weight (kg), size of the VSD, size of the ASD and shunt direction of the defect site were significantly correlated with PMV after surgery. The risk prediction model was established in combination with the corresponding regression coefficients (Y=-0.961-0.208*X1+0.147*X2+0.095*X3+1.045*X4)[X1: weight (kg), X2: size of the VSD (cm), X3: size of the ASD (cm), X4: shunt direction of the defect site (1: left to right; 2: bi-directional shunt)], and the area under the curve of the model was 0.853,95%CI:0.812-0.895 (ROC curve). The results are shown in figure 2A.

4.3 Verify the prediction model

In another cardiac centre, we adopted the same inclusion and exclusion criteria to collect clinical data from 164 paediatric patients and entered these data into the model for verification. The general information of the 164 patients is shown in table 3. The area under the ROC curve was 0.843, 95%CI:0.751-0.934 (Figure 2B). The calibration plots presented an excellent agreement in the total samples and random subsamples between the nomogram prediction and actual observation for PMV(Figure 3). This proves that our prediction model had good scalability.

4.4 Visualization operation of the prediction model – nomogram

Finally, we used R language to draw the nomogram and visualize the prediction model. The result is shown in figure 4. We use the data of a child in validation data to illustrate the use of the model: a 2-year-old male child with a weight of 13Kg, diagnosed as a ventricular septal defect, and with a defect diameter of 3.0cm and shunt left to right, and no other congenital heart disease . According to the prediction model Y=0.961-0.208×13.0+0.147×3.0+0.095×0+1.045×1=-0.257. When Y=-0.257, the value of the vertical corresponding “probabilities” line is at 0.2, which means that the probability of PMV in this child is about 20%.

5 Discussion

Postoperative PMV in paediatric patients with CHD indicates an increased risk of death[10]. We selected a heart centre with rich experience in paediatric CHD surgery (more than 500 operations per year) to conduct this retrospective study, with the purpose of assessing the available preoperative clinical data in order to predict the risk of postoperative PMV. This prediction would be significant if risk factors could be actively corrected preoperatively in order to reduce PMV risk.

With the use of single-factor regression at the beginning of the study, we analysed all factors that were possibly associated with postoperative PMV, including the patient's age, weight, height, type of defect, defect size, and so on, with more than 30 factors. Finally, we focused on 18 factors ($P<0.05$). Taking into account the correlation between all factors, as well as the statistical requirements of sample size and the results of previous studies[6-8,10], we ultimately selected 9 factors (table 2), including weight and shunt direction, to conduct multivariate logistic regression analysis and build a prediction model.

The correlation between body weight and postoperative ventilator-assisted ventilation time in

children has been confirmed by almost all relevant studies [6-8,10], and our study also confirmed this close correlation (ORadj: 0.81, 95% CI: 0.73-0.91). Right-to-left shunting in children is due to the continuous increase in pulmonary hypertension, and most of these children cannot obtain anatomical correction. In our study, there were no children with right-to-left shunting. However, bidirectional shunting is a factor that requires surgeons to determine whether they can perform primary anatomical correction. In this study, there were 63 children with bidirectional shunting, among whom 47 had mainly left-to-right shunting, 16 had mainly right-to-left shunting, and all patients had combined severe pulmonary hypertension. Preoperatively, pulmonary artery catheters were assessed to ensure that they would be able to be placed during radical surgery. Primary anatomical correction resulted in PMV after surgery in 33 children. It can be seen from our prediction model that the shunt direction of the defect had the greatest weight on the prediction result. For these patients, we routinely treated pulmonary artery hypertension preoperatively, but whether this treatment reduces the risk of PMV is worth further consideration.

VSDs, especially large VSDs, are highly associated with increased PH and decreased pulmonary circulation blood flow after repair, prompting surgeons to carefully remove the endotracheal tube. Of course, most of the VSDs included in our study were not suitable for interventional closure therapy; age is an important factor[11], and some of the reasons for subaortic or infracristal VSDs (type II Kirklin) are obviously descending aortic valves, large defects, and the combination of other heart defects [12-13]. Whether these factors influenced our prediction results is unknown. This is one of the shortcomings of the study. Additionally, in terms of the influence of ASDs on postoperative outcomes, mostly on the basis of the existence of VSDs and ASDs alone, there were only 3 cases of postoperative PMV in our study; however, when considering the coexistence of VSDs and ASDs in terms of the issue of anatomical correction surgery, ASDs were alleviated after repairing the right heart load. At the same time, pulmonary hypertension (with a lack of atrioventricular defects in children with different levels of pulmonary artery pressure) could also reduce pulmonary blood flow, and this is likely the main cause of this kind of PMV in children.

Although the CBP time was not known preoperatively, most studies[14,15] confirmed that CBP intraoperative factors were associated with postoperative PMV, so we also analysed the relationship between the CBP time and postoperative PMV. It was found that there was no correlation between the CBP time and postoperative PMV (P=0.57). This may be because we selected data from a single experienced heart surgery centre. The CBP time was closely related to the surgeon's experience with the level of technology.

This study only predicted risk factors for children with simple CHD, rather than for all paediatric patients with CHD, because we believe that the availability of anatomical correction for CHD is fundamentally different in terms of the perioperative risks and long-term prognoses[14-16].

As a retrospective study, in order to balance the sample data, we used data from a single experienced centre to construct the prediction model, which inevitably led to limitations of

the study. Another limitation is the stability of prediction results in different regions, such as the difference between plateau and non-plateau regions[17]. In addition, whether improvements in the risk factors found in the prediction model will definitely reduce the incidence of adverse events is also lacking evidence.

Therefore, we plan to design a multicentre prospective clinical study based on this study, hoping to compensate for the deficiencies in this study. We hope that future studies can reduce the incidence of PMV and promote the rapid recovery of CHD in children by improving the risk factors from the prediction model.

6 Conclusion

In an experienced paediatric cardiac surgery centre, for children with simple congenital heart disease repaired under CBP, weight, atrioventricular size and shunt direction are the main factors influencing the occurrence of PMV after surgery. The prediction model established based on this study is reliable for small sample validation.

7 Abbreviations

CHD:congenital heart diseas, PMV:Prolonged mechanical ventilation,CBP :cardiopulmonary bypass, VSD:Ventricular septal defect, ASD:Atrial septal defect, PDA:Patent ductus arteriosus, PH: pulmonary hypertension, AVP:Aortic valve prolapse, DCRV:double-chambered right ventricle, PS:pulmonary stenosis, DS:Down's syndrome

Added

Most of the children included in this study came from poor families in remote areas of China, and their treatment was fully funded by charities such as the He Tao Xiang charitable foundation. I would like to thank the sponsors of these charities for their selfless dedication over the years. I would also like to thank the staff of the Ministry of Social Work, such as Ms. Rong-hua Jiang, for their selfless dedication.

Reference

[1] Duca LM, Pyle L, Khanna AD, et al. Estimating the prevalence of congenital heart disease among adolescents and adults in Colorado adjusted for incomplete case ascertainment. Am Heart J. 2020;221:95–105. doi:10.1016/j.ahj.2019.11.012

[2] Mat Bah MN, Sapian MH, Jamil MT, Abdullah N, Alias EY, Zahari N. The birth prevalence, severity, and temporal trends of congenital heart disease in the middle-income country: A population-based study. Congenit Heart Dis. 2018;13(6):1012–1027. doi:10.1111/chd.12672

[3] Pasquali SK, Gaies M, Banerjee M, et al. The Quest for Precision Medicine: Unmeasured Patient Factors and Mortality After Congenital Heart Surgery. Ann Thorac Surg. 2019;108(6):1889–1894. doi:10.1016/j.athoracsur.2019.06.03

[4] Kalfa D, Torres AJ. Indications and results for hybrid interventions in patients with congenital heart disease [published online ahead of print, 2019 Sep 3]. Arch Cardiovasc Dis. 2019;S1875-2136(19)30136-6. doi:10.1016/j.acvd.2019.06.006

[5] Farooqi M, Stickley J, Dhillon R, et al. Trends in surgical and catheter interventions for isolated congenital shunt lesions in the UK and Ireland. Heart. 2019;105(14):1103–1108. doi:10.1136/heartjnl-2018-314428

[6] Delaney AE, Dadlez NM, Marshall AC. Alternative approach to pediatric cardiac quality assessment for low-volume centers. Congenit Heart Dis. 2019;14(4):665–670. doi:10.1111/chd.12821

[7] Luo Q, Su Z, Jia Y, et al. Risk Factors for Prolonged Mechanical Ventilation After Total Cavopulmonary Connection Surgery: 8 Years of Experience at Fuwai Hospital [published online ahead of print, 2019 Nov 2]. J Cardiothorac Vasc Anesth. 2019;S1053-0770(19)31118-8.

[8] Tabib A, Abrishami SE, Mahdavi M, Mortezaeian H, Totonchi Z. Predictors of Prolonged Mechanical Ventilation in Pediatric Patients After Cardiac Surgery for Congenital Heart Disease. Res Cardiovasc Med. 2016;5(3):e30391. Published 2016 Jul 20. doi:10.5812/cardiovascmed.30391

[9] Ammash NM, Warmes CA. Ventricular septal defects in adults. Ann Intern Med. 2001;135(9):812-824.

[10] Alrddadi SM, Morsy MM, Albakri JK, et al. Risk factors for prolonged mechanical ventilation after surgical repair of congenital heart disease. Experience from a single cardiac center. Saudi Med J. 2019;40(4):367–371. doi:10.15537/smj.2019.4.23682

[11] Diab KA, Cao QL, Mora BN, Hijazi ZM. Device closure of muscular ventricular septal defects in infants less than one year of age using the Amplatzer devices: feasibility and outcome. Catheter Cardiovasc Interv, 2007, 70(1):90–97.

[12] Butera G, Chessa M, Carminati M. Percutaneous closure of ventricular septal defects. State of the art. J Cardiovasc Med (Hagerstown). 2007;8(1):39–45. doi:10.2459/01.JCM.0000247434.59451.d7

[13] Carminati M, Butera G, Chessa M, et al. Transcatheter closure of congenital ventricular septal defect with Amplatzer septal occluders. Am J Cardiol. 2005;96(12A):52L–58L. doi:10.1016/j.amjcard.2005.09.068

[14] Traiber C, Piva JP, Fritsher CC, et al. Profile and consequences of children requiring prolonged mechanical ventilation in three Brazilian pediatric intensive care units. Pediatr Crit

Care Med. 2009;10(3):375–80.
[15] Buys R, Van De Bruaene A, De Meester P, et al. Predictors of mid-term event-free survival in adults with corrected tetralogy of Fallot. Acta Cardiol. 2012;67(4):415–421. doi:10.1080/ac.67.4.2170682
[16] Shafer KM, Opotowsky AR, Rhodes J. Exercise testing and spirometry as predictors of mortality in congenital heart disease: Contrasting Fontan physiology with repaired tetralogy of Fallot. Congenit Heart Dis. 2018;13(6):903–910. doi:10.1111/chd.12661
[17] González-Andrade F, Echeverría D, López V, Arellano M. Is pulse oximetry helpful for the early detection of critical congenital heart disease at high altitude?. Congenit Heart Dis. 2018;13(6):911–918. doi:10.1111/chd.12654

Table 1: 585 cases of pediatric patients eligible and eventually included in this study.

Factors	No-PMV(<24h) , n=492	PMV(>24h),n=93	P values
Gender			0.14
Male	258	41	
Female	234	52	
Age(years)	3.79±3.50	1.48±2.37	<0.001
Weight(kg)	14.59±9.98	7.62±4.73	<0.001
Height(cm)	97.48±24.95	70.72±19.21	<0.001
Diagnosis			<0.001
VSD	267	36	
ASD	94	3	
PDA	16	1	
VSD+ASD	74	42	
VSD+PDA	17	6	
VSD+ASD+PDA	11	3	
ASD+PDA	13	2	
With PH	184	64	<0.001
With DCRV	17	4	0.688
With PS	45	9	0.886
With AVP	62	5	0.007
With DS	15	5	0.349
With Favism	15	3	0.928
Shunt Direction			<0.001
Left to right shunt	462	60	
Bi-directional shunt	30	33	
Size of VSD(mm)	5.85±4.77	8.99±4.09	<0.001
Size of ASD(mm)	4.59±8.09	2.81±5.09	0.006
Pressure difference	34.20±1.81	30.89±3.41	<0.001
MPA	16.82±4.84	14.97±4.51	0.001
BP	114.42±20.26	128.76±18.56	<0.001
Time of CBP	57.14±22.96	59.13±32.00	0.57
Death	0	2	\

Abbreviations:PMV:Prolonged mechanical ventilation,VSD:Ventricular septal defect, ASD:Atrial septal defect, PDA:Patent ductus arteriosus, PH: pulmonary hypertension, DCRV:double-chambered right ventricle, PS:pulmonary stenosis, AVP:Aortic valve prolapse DS:Down's syndrome,MPA: Main pulmonary artery,HR: Heart rate,CBP :cardiopulmonary bypass

Table 2 Univariate and multivariate analysis of factors related to the occurrence of PMV

	Univariate OR(95%CI)	P values	Multivariate OR(95%CI)	P values
Weight	0.75(0.70-0.81)	<0.001	0.81(0.73-0.91)	<0.001
Size of VSD	1.14(1.10-1.20)	<0.001	1.16(1.03-1.30)	0.013
Size of ASD	0.96(0.93-1.00)	0.045	1.10(1.00-1.20)	0.042
Diagnosis	1.32(1.17-1.50)	<0.001	1.10(0.90-1.34)	0.341
PH	2.03(1.68-2.45)	<0.001	0.95(0.68-1.33)	0.765
Shunt Direction	8.47(4.82-14.87)	<0.001	2.84(1.32-6.11)	0.007
Pressure difference	0.96(0.96-0.97)	<0.001	0.99(0.97-1.00)	0.126
BP	1.04(1.02-1.05)	<0.001	1.00(0.98-1.02)	0.948
MPA	0.90(0.85-0.96)	0.001	0.95(0.86-1.04)	0.232

Figure 1: Flowchart for screening eligible patients in this study.

Figure 2A: The established model was used to diagnose the risk of postoperative PMV in 585 patients included in the study, and the ROC curve proved that the diagnosis was consistent(AUC=0.853). B: A set of separate data including 162 patients from another experienced heart center were confirmed the value of prediction model. ROC curve proved that the diagnosis was scalability(AUC=0.843)

Figure 3: The calibration curves for predicting patient at risk of PMV for the Study of 585 cases. Nomogram-predicted risk of PMV is plotted on the x-axis; actual risk of PMV is plotted on the y-axis. A plot along the 45-degree line would indicate a perfect calibration model in which the predicted probabilities are identical to the actual outcomes.

Figure 4: Nomogram of PMV after anatomical repair assisted by CBP for patients with simple CHD. Y= -0.961-0.208*X1+0.147*X2+0.095*X3+1.045*X4, X1: weight (kg), X2: size of the VSD (cm), X3: size of the ASD (cm), X4: shunt direction of the defect site (1: left to right; 2: bi-directional shunt).