

Down syndrome and postoperative complications after paediatric cardiac surgery: a propensity-matched analysis

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Received 22 December 2012; received in revised form 2 May 2013; accepted 22 May 2013

Abstract

OBJECTIVES: The incidence of congenital heart disease is ~50%, mostly related to endocardial cushion defects. The aim of our study was to investigate the postoperative complications that occur after paediatric cardiac surgery.

METHODS: Our perioperative data were analysed in paediatric patients with Down syndrome undergoing cardiac surgery. We retrospectively analysed the data from 2063 consecutive paediatric patients between January 2003 and December 2008. After excluding the patients who died or had missing data, the analysed database (before propensity matching) contained 129 Down patients and 1667 non-Down patients. After propensity matching, the study population comprised 222 patients and 111 patients had Down syndrome.

RESULTS: Before propensity matching, the occurrences of low output syndrome (21.2 vs 32.6%, $P = 0.003$), pulmonary complication (14 vs 28.7%, $P < 0.001$) and severe infection (11.9 vs 22.5%, $P = 0.001$) were higher in the Down group. Down patients were more likely to have prolonged mechanical ventilation [median (interquartile range) 22 (9–72) h vs 49 (24–117) h, $P = 0.007$]. The total intensive care unit length of stay [6.9 (4.2–12.4) days vs 8.3 (5.3–13.2) days, $P = 0.04$] and the total hospital length of stay [17.3 (13.3–23.2) days vs 18.3 (15.1–23.6) days, $P = 0.05$] of the Down patients were also longer. Mortality was similar in the two groups before (3.58 vs 3.88%, $P = 0.86$) and after (5.4 vs 4.5%, $P = 1.00$) propensity matching. After propensity matching, there was no difference in the occurrence of adverse events.

CONCLUSIONS: After propensity matching Down syndrome was not associated with increased mortality or complication rate following congenital cardiac surgery.

Keywords: Down syndrome • Paediatrics • Predictors • Paediatric cardiac surgery • Congenital heart disease

INTRODUCTION

Down syndrome (DS) is a genetic disease that is also known as trisomy of the 21st chromosome and is characterized by various congenital defects, organic disorders, dysmorphic features and other health-related problems [1, 2]. This medical condition is associated with an increased incidence of congenital heart disease compared with the healthy, genetically normal population [3].

DS patients are most commonly affected by acyanotic heart lesions. Pulmonary hypertension is a frequent complication of patients with DS and congenital heart defects that require surgical treatment [4]. Cardiac surgery is not contraindicated, as previously suggested, and can be performed with very good results [5]. Previous studies have reported a higher occurrence of postoperative complications [6].

However, DS patients have decreased buffering of metabolic derangements and are predisposed to developing leukaemia and other myeloproliferative disorders [7].

The purpose of this study was to use a propensity-matched analysis to compare the postoperative morbidity and mortality of paediatric patients with and without DS who underwent heart surgery. Our hypothesis was that this chromosomal condition was associated with increased mortality and morbidity.

METHODS

A total of 2063 consecutive patients (<18 years) undergoing heart surgery and admitted to our cardiac intensive care unit (ICU) between January 2003 and December 2008 were screened after

Institutional Review Board approval (TUKEB 567/2012). The board waived the need for parental informed consent. After excluding the cases with missing data ($n = 366$) and the patients who died during surgery ($n = 27$, all were non-Down patients), 1667 patients (1538 control vs 129 with DS) remained for further analysis (Fig. 1). We analysed the data from 298 neonates, 570 infants and 799 children. The diagnosis of the condition was always based on physical characteristics and the presence of an extra chromosome 21.

A propensity-matched statistical analysis allowed for the analysis of patients with similar characteristics. The propensity scores for DS were estimated using a non-parsimonious multivariable logistic regression model with 14 baseline covariates according to our earlier investigation (Fig. 2) [8]. The cardiac surgical procedures were graded by applying the risk adjustment for congenital heart surgery (RACHS) score [9]. To quantify the amount of cardiac support, we calculated the modified inotropic score as described by Wernovsky: [dopamine ($\mu\text{g}/\text{kg}/\text{min}$) + dobutamine ($\mu\text{g}/\text{kg}/\text{min}$) + 100 \times epinephrine ($\mu\text{g}/\text{kg}/\text{min}$) + 100 \times norepinephrine ($\mu\text{g}/$

kg/min) $\times 20 \times$ milrinone ($\mu\text{g}/\text{kg}/\text{min}$)]. Mortality was defined as death from any cause.

The combined endpoint of the study was defined as death after arrival at the ICU, including the patients who died after having been transferred to another hospital or after developing any of the following complications: *postoperative low output syndrome* (LOS) (clinical signs: tachycardia, oliguria, cold extremities or cardiac arrest and an increase in base deficit >4 on two consecutive blood gas measurements); *pulmonary complication*, defined as non-infectious, non-vascular oxygenation problems (atelectasia, pneumothorax, chylothorax, phrenic paresis); *renal failure*, the need for peritoneal dialysis or haemodialysis; *infections*, catheter-related and deep sternal wound infection, positive blood culture or sepsis. *Neurological events*, such as convulsion without prior history, haemorrhage or infarction demonstrated on cranial imaging, were also included in the composite outcome.

In the statistical analysis, for categorical variables, results are expressed as counts and percentages and means and standard deviations (SDs) for categorical and continuous variables, respectively. Patients with missing data on baseline covariates and clinical outcomes were excluded from the sample. Comparisons of the demographic and perioperative differences between the patients were based on the χ^2 -test, Fisher's exact test and t -tests, as appropriate. Because there were differences in the baseline characteristics, the DS and control groups were not comparable with respect to important covariates. To minimize differences and overcome the bias resulting from the study design, we constructed a propensity-score model for having DS or not. The model's reliability and predictive ability were measured with the Hosmer-Lemeshow test and the c -index, respectively. The receiver operating characteristic curve's c -index (area under the curve) was 0.8345, and the Hosmer-Lemeshow C statistic was 11.3 with a P -value of 0.183 (8 degrees of freedom).

We computed the propensity score using a non-parsimonious multivariable logistic regression model with DS as the dependent variable and all the risk factors listed in Tables 1 and 2 as predictor variables. The DS patients were matched to patients without this genetic disorder with similar propensity scores. We used a 1:1 nearest-neighbour greedy matching without replacement to form pairs using callipers of width equal to 0.2 of the SD of the logit of the propensity score [11]. The 111 matched pairs were analysed for differences in the baseline characteristics and outcome

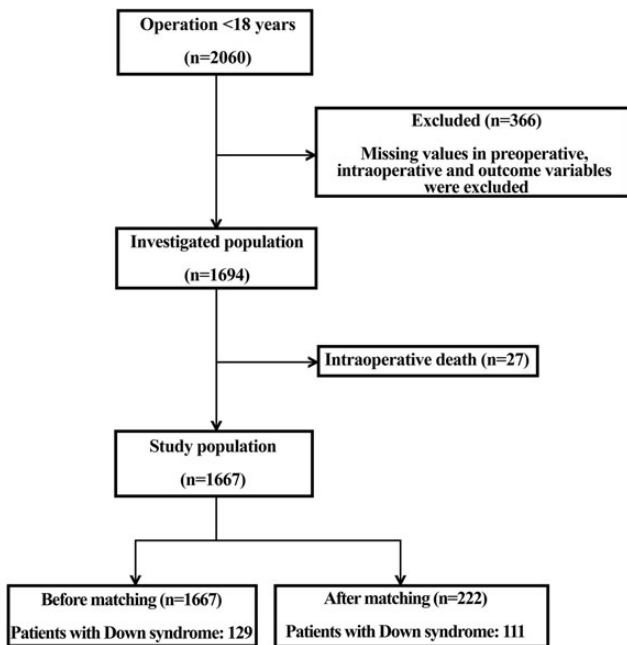


Figure 1: Study population before and after matching.

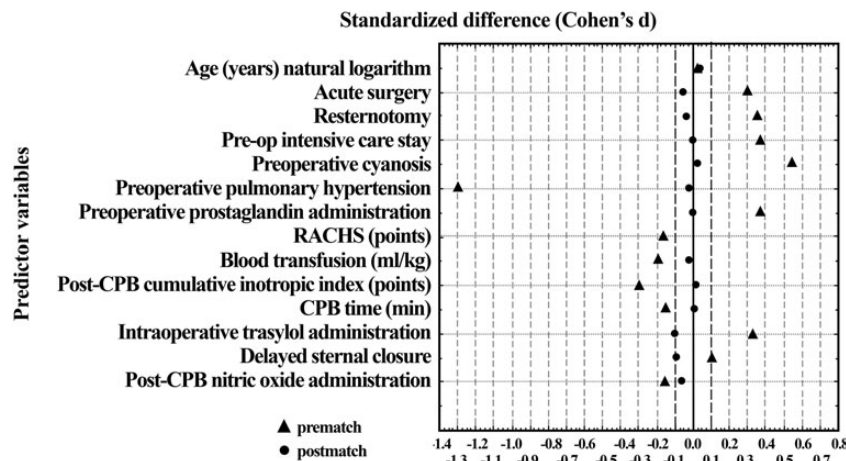


Figure 2: Standardized difference values of the 14 baseline covariates. RACHS: risk adjustment for congenital heart surgery; CPB: cardiopulmonary bypass.

Table 1: Predictor variables before matching

	Control (n = 1538)		Down (n = 129)		P-value
	Median (n)	IQR (%)	Median (n)	IQR (%)	
Age (years) (natural logarithm)	-0.005	-1.3 to 1.6	-0.5	-0.8 to 0.06	0.54
Intensive care stay	325	21.1	8	6.2	<0.001
Cyanosis	520	33.8	11	8.5	<0.001
Prostaglandin usage	218	14.2	2	1.6	<0.001
Pulmonary hypertension	203	13.2	76	58.9	<0.001
RACHS					
1	240	15.6	5	3.9	<0.001
2	710	46.2	59	45.7	
3	455	29.6	64	49.6	
4	107	7.0	0	0.00	
6	26	1.7	1	0.8	
Acute surgery	200	13.0	4	3.1	<0.001
Resternotomy	332	21.6	9	7.0	<0.001
Intraoperative aprotinin administration	337	21.9	11	8.5	<0.001
Blood transfusion (ml/kg)	16	0 to 36.4	33.3	20 to 41.7	<0.001
Cardiopulmonary bypass time (min)	67	41 to 115	90	65 to 115	0.03
Cumulative inotropic index	4	0 to 16	11	6 to 21	<0.001
Nitric oxide	107	7.0	14	10.9	0.10
Delayed sternal closure	227	14.8	14	10.9	0.23

The data are presented as number and occurrence (%) or as median and interquartile range (IQR). Significant values are bold faced. RACHS: risk adjustment for congenital heart surgery.

Table 2: Predictor variables after matching

	Control (n = 111)		Down (n = 111)		P-value
	Median (n)	IQR (%)	Median (n)	IQR (%)	
Age (years) (natural logarithm)	-0.5	-1.1 to 1.2	-0.5	-0.8 to 0.3	0.85
Intensive care stay	8	7.2	8	7.2	1.00
Cyanosis	12	10.8	11	9.9	1.00
Prostaglandin usage	2	1.8	2	1.8	1.00
Pulmonary hypertension	57	51.4	58	52.3	1.00
RACHS					
1	11	9.9	5	4.5	1.00
2	54	48.7	59	53.2	
3	39	35.1	46	41.4	
4	6	5.4	0	0.00	
6	1	0.9	1	0.9	
Acute surgery	3	2.7	4	3.6	1.00
Resternotomy	8	7.2	9	8.1	1.00
Aprotinin	8	7.2	11	9.9	0.60
Blood transfusion (ml/kg)	27	0 to 44.4	31.3	15.3 to 41.6	0.89
Cardiopulmonary bypass time (min)	72	55 to 117	81	61 to 113	1.00
Cumulative inotropic index	10	0 to 22	10	4 to 19	0.90
Nitric oxide	8	7.2	10	9.0	0.79
Delayed sternal closure	10	9.0	13	11.7	0.53

Data are presented as number and incidence (%) or median and interquartile range (IQR). RACHS: risk adjustment for congenital heart surgery.

variables. The outcomes and measured covariates were compared between groups with a paired *t*-test for continuous variables and McNemar's test for the categorical data. To evaluate the success of balancing the baseline characteristics between the matched groups, standardized differences were estimated [12]. Across the 14 baseline covariates, the standardized differences were between -0.1 and 0.1. Figure 2 indicates that the mean and prevalence of

the variables were similar between the two groups and covariates were appropriately balanced [13].

All tests were two-sided. We considered $P < 0.05$ significant. Analyses were conducted with Stata SE 12 (Stata, College Station, TX, USA), the SPSS 16.0 statistical software (SPSS, Inc., Chicago, IL, USA) and the STATISTICA 8.0 data analysis software system (StatSoft, Inc., Tulsa, OK, USA).

Table 3: Outcome variables before matching

	Control (n = 1538)		Down (n = 129)		P-value
	Median (n)	IQR (%)	Median (n)	IQR (%)	
Combined outcome	246	16.0	34	26.4	0.002
Death	55	3.6	5	3.9	0.86
Low output syndrome	326	21.2	42	32.6	0.003
Mechanical ventilation (h)	22	9–72	49	24–117	0.007
Pulmonary complication	215	14.0	37	28.7	<0.001
Renal failure	88	5.7	9	7.0	0.56
Severe infection	183	11.9	29	22.5	0.001
Neurological event	35	2.3	0	0.00	0.08
ICU stay (days)	6.9	4.2–12.4	8.3	5.3–13.2	0.04
Hospital stay (days)	17.3	13.3–23.2	18.3	15.1–23.6	0.05

Data are presented as number and incidence (%) or median and inter-quartile range (IQR). Significant values are bold faced. ICU: intensive care unit.

Table 4: Outcome variables after matching

	Control (n = 111)		Down (n = 111)		P-value
	Median (n)	IQR (%)	Median (n)	IQR (%)	
Combined outcome	25	22.5	27	24.3	0.76
Death	6	5.4	5	4.5	1.00
Low output syndrome	32	28.9	35	31.5	0.67
Mechanical ventilation (h)	32	11–75	46	23–114	0.12
Pulmonary complication	23	20.7	31	27.9	0.22
Renal failure	5	4.5	6	5.4	1.00
Severe infection	20	18.0	22	19.8	0.74
Neurological event	3	2.7	0	0.0	0.25
ICU stay (days)	7.2	4.4–11	8.2	5.3–12.9	0.15
Hospital stay (days)	17.5	14.2–23.7	18.1	14.3–23.3	0.27

Data are presented as number and incidence (%) or median and inter-quartile range (IQR). ICU: intensive care unit.

RESULTS

During the 6-year period, 2060 patients underwent operations; 366 patients (17.8%) had missing values and 27 patients (1.3%) died intraoperatively. Before propensity matching in the study population of 1667 patients, 129 patients (7.74%) had DS. After propensity matching, we had 222 patients in the study population and 111 (50.0%) had DS.

The propensity score matching yielded 111 pairs of patients in our unbiased database. There were no differences in the baseline characteristics between the pairs in our balanced system. The standardized difference was used to assess the balance of the covariates because it did not depend on the size of the sample. A standardized difference of less than the absolute value of 10% was used to indicate that the preoperative and perioperative characteristics across groups were comparable. The mean propensity score of the Down and the control groups were 0.210 and 0.220, respectively.

Before propensity matching, the patients with DS had higher morbidity values; however, there were no significant differences between the non-Down and Down groups with regard to mortality before and after propensity matching [before, $n = 55$ (3.58%) vs

5 (3.88%); after, $n = 6$ (5.41%) vs 5 (4.5%)] (Tables 3 and 4). Further demographic and perioperative characteristics before and after matching are presented in Tables 1 and 2.

Significant differences were detectable before propensity matching between the Down and non-Down groups regarding nearly all of the predictor variables. More children were admitted preoperatively to the ICU in the non-Down group and they were more likely to have preoperative cyanosis or needed prostaglandin before the operation. We found more patients with preoperative pulmonary hypertension in the Down group. Non-Down patients needed acute surgery more frequently than the children with DS. A greater amount of aprotinin was given to the non-Down patients intraoperatively. Down patients required more blood transfusions, had longer cardiopulmonary bypass times and received higher amounts of inotropic drugs than those without the disorder. Down children had mostly primary operations. Patients with DS underwent less complex surgeries according to their RACHS points (Table 1). Before matching, the occurrence of cyanotic heart disease was lower in patient with DS [15 (11.6%) vs 364 (23.6%), $P = 0.002$, in Down vs non-Down patients, respectively]. In the matched population, the occurrence of cyanotic disease was similar ($P = 0.88$). There were no significant

Table 5: Laboratory values after matching

	Preoperative			DOS			POD 1			POD 2		
	Control (n = 111)	Down (n = 111)	P-value	Control (n = 111)	Down (n = 111)	P-value	Control (n = 111)	Down (n = 111)	P-value	Control (n = 111)	Down (n = 111)	P-value
C-reactive protein (IU/l)	121.7 (19.7)	122.2 (19.5)	0.84	105.6 (19.7)	121.0 (18.8)	0.04	45.8 (19.8)	53.0 (30.5)	0.19	70.0 (45.3)	89.6 (55.7)	0.19
Haemoglobin (g/l)	319.9 (94.4)	283.9 (97.0)	0.008	8.2 (2.3)	7.6 (2.5)	0.10	113.0 (17.7)	117.9 (13.3)	0.04	108.3 (13.6)	114.0 (13.0)	0.006
Platelet count (10 ⁹ /l)	79.9 (29.1)	66.6 (20.5)	<0.001	-5.4 (2.4)	-6.0 (2.3)	0.14	165.3 (76.5)	143.1 (83.7)	0.02	156.0 (81.5)	126.8 (78.5)	0.01
Creatinine clearance (ml/min)							69.3 (29.0)	59.5 (19.4)	0.002	75.2 (35.3)	58.2 (22.5)	0.02
Mean blood glucose (mmol/l)							5.9 (1.5)	5.8 (1.5)	0.51	5.4 (1.5)	5.8 (1.5)	0.08
Maximum blood glucose (mmol/l)							7.9 (2.6)	7.5 (1.9)	0.16	6.8 (2.1)	7.4 (2.8)	0.06
Base excess (mmol/l)							-3.4 (2.5)	-3.8 (2.5)	0.22	-0.9 (2.2)	-1.6 (2.9)	0.07

Significant values are bold faced.
DOS: day of surgery; POD: postoperative day.

differences in the postoperative mortality and composite mortality. Table 2 shows that after propensity matching of the above-mentioned predictive values, the differences disappeared. We could not determine any significant variance in our statistically balanced system. According to our data (after matching), in the postoperative period, 48 patients (46%) with DS received thyroxin through the nasogastric tube, while only 29 patients (26%) of the control group ($P=0.008$) received the medication. Additionally, only 8 patients (7%) received insulin infusion compared with 20 patients (18%) in the control group ($P=0.018$). Steroid administration was similar in the two groups ($P=0.99$).

Tables 3 and 4 present the outcomes of the patients before and after propensity matching. Before propensity matching, the Down patients had higher mortality and morbidity rates than the non-Down patients. The occurrence of LOS, pulmonary complication, renal failure and severe infection was higher in the Down group. Down patients were also more likely to undergo prolonged mechanical ventilation. The incidence of neurological events was higher in the non-Down group but the variation was not significant. The lengths of the ICU and hospital stays were also longer in the Down group than in the case of control patients. After propensity matching, there was no significant variation detectable between the Down and control groups (Table 4).

Table 5 shows the measured perioperative laboratory values of both groups (control and DS) after propensity matching. The haemoglobin levels in the Down group were higher in the postoperative period. The platelet counts were lower in the DS

Table 6: Procedures by patient group after matching

Procedure	Down	Control	P-value
ASD repair, patch	2	5	0.44
AVSD repair, intermediate (transitional)	7	0	0.01
AVSD repair, partial (incomplete)	7	0	0.01
AVSD repair, complete	30	19	0.07
Coarctation repair, end-to-end	3	4	1
DORV, intraventricular tunnel repair	1	7	0.06
Norwood procedure	1	0	1
PA banding	3	4	1
PDA closure, surgical	3	3	1
RVOT procedure	1	2	1
Shunt, systemic-to-pulmonary, MBTS	3	2	1
TOF repair	6	6	1
Valve replacement, mitral	2	1	1
Valvuloplasty, mitral	7	5	0.55
Valvuloplasty, tricuspid	5	0	0.06
VSD repair, patch	30	31	0.88
Aortic root repair	0	1	1
DKS	0	1	1
Double chamber	0	1	1
Fontan.	0	4	0.12
PAPVC	0	3	0.24
Ross	0	7	0.01
TAC	0	2	0.49
TAPVC	0	3	0.24

ASD: atrial septal defect; AVSD: atrioventricular septal defect; DORV: double outlet right ventricle; PA: pulmonary artery; PDA: persistent ductus arteriosus; RVOT: right ventricle outflow tract; MBTS: modified Blalock-Taussig shunt; TOF: tetralogy of Fallot; VSD: ventricular septal defect; DKS: Damus-Kaye-Stansel procedure; PAPVC: partial anomalous pulmonary venous connection; TAC: transverse aortic constriction; TAPVC: total anomalous pulmonary venous connection.

patients. Creatinine clearance was lower in the Down patients during the entire perioperative period.

Table 6 shows the procedures by the two groups after propensity matching. The only differences observable were in the cases when no match was found, namely when transitional and partial atrioventricular septal defect (AVSD) repair, tricuspid valvuloplasty and Ross procedure were performed.

DISCUSSION

We found that patients with DS had higher occurrences of postoperative complications. Using propensity score methods, we matched a large number of patients who had DS in a paediatric cardiac surgical population to a group of patients (comparable with respect to every measured covariate) who did not suffer from this disorder. After the propensity matching, there were no significant differences in postoperative complications and mortality between the Down and non-Down patients. More patients with DS were treated with thyroxin in the postoperative period. We found lower levels of platelets and creatinine clearance in the patients with DS.

The cumulative mortality of patients with DS after cardiac surgery was comparable or even lower than in the patients with normal karyotypes after congenital heart surgery [14]. If open heart surgery was performed, a prolonged cardiopulmonary bypass time was associated with a higher mortality risk [15]. Many things depend also on the right timing of surgery, which is sometimes different in Down and non-Down patients. For instance, the repair of AV canal within 4 months of age leads to fewer complications in patients with DS compared with others (where the achievement of competent valves is more difficult to obtain). The mortality data were adjusted in our analysis, but the occurrence of prolonged cardiopulmonary bypass time was more likely in the patients with DS before matching.

Another point to be considered in children with DS is that they frequently have LOS, which adversely affects surgical outcomes [16]. Indeed, these differences could also be detected in our study population; the patients with DS had higher rates of low cardiac output syndrome and pulmonary complications. However, our results indicated that these adverse events may be caused by the degree of the operation complexity and the intraoperative variables, such as inotropic dose or the amount of transfusion. After adjusting for the intraoperative variables, the occurrence of postoperative complications was similar in the Down and control groups. In accordance with our findings, pain relief and the duration of mechanical ventilation did not differ in the patients with DS vs the controls [17].

The occurrence of postoperative renal failure requiring dialysis (haemodialysis or peritoneal dialysis) was similar in both groups, despite the lower pre- and postoperative creatinine clearance in the DS patients. Previous reports have not suggested frequent renal dysfunction in patients with DS [18]. The lower creatinine clearance in our study population might have been caused by cardio-renal syndrome or previous anticongestive medications [19]. The patients with DS spent significantly more time in the ICU and stayed significantly longer in the hospital, but this variance also disappeared after propensity matching. Other studies have also demonstrated prolonged hospital stays with Down patient hospitalized in general ICUs. [2].

The incidence of infective complications was frequent in the Down group. This observation is in agreement with the results of

other studies [20]. Children with DS are at high risk of thyroid dysfunction; subclinical hypothyroidism is the most common thyroid abnormality in these patients. Frequent infections are presumably caused by impaired immune responses, and the incidence of autoimmunity, including hypothyroidism, is increased [21]. In our study population, DS patients were more frequently treated with thyroxin. This difference might explain why the occurrence of infections was comparable with the propensity-matched control population. The decreased buffering of metabolic processes results in increased insulin resistance. Therefore, diabetes mellitus develops in many affected patients [22]. In our paediatric patients, we observed a tendency towards lower base excess, but it did not reach significance.

Isolated thrombocytopenia, thrombocytosis and several other haematological disorders can be observed in DS patients [23]. In the unmatched cohort, the need for intraoperative blood transfusions was significantly higher in DS patients. In our population, the postoperative haemoglobin levels were significantly higher and the platelet count was significant lower in the Down patients after propensity matching. Because we matched the patients according to their pre- and intraoperative variables, we could not compare the need for intraoperative transfusion. Our previous study did not find an independent relationship between DS and transfusion [24].

Our study had limitations. The retrospective analysis did not allow of an investigation into causes and consequences. However, our proprietary hospital database recorded prospective clinical, diagnostic and outcome data on all the paediatric ICU patients since January 2003. This was a single-centre study and the database comprised patients of different ages with heterogeneous congenital heart defects, which improves the generalizability of the study. Our analysis applied propensity score matching, which can balance bias based on heterogeneity of patient and operation characteristics.

In conclusion, we found that after propensity matching, the perioperative values we studied did not influence the outcomes of DS patients and there were no significant differences between the Down and non-Down groups with regard to the rates of postoperative complications or mortality after matching. This statistical method, which used similar values for the variables, can play an important role in identifying the differences between control and investigated groups.

Conflict of interest: none declared.

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