SURGICAL VOLUME AND CENTER EFFECTS ON EARLY MORTALITY AFTER PEDIATRIC CARDIAC SURGERY: 25-YEAR EXPERIENCE FROM THE PEDIATRIC CARDIAC CARE CONSORTIUM

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Dedication

This thesis is dedicated to Drs Alvin Chin, Jonathan Epstein, William Norwood and James Moller who gave me the tools to understand, how the heart is formed, why it can take so many different forms, why it sometimes fails, the many different ways to mend a “broken” heart and assess how effective the repair was.

Abstract

Context: Mortality after pediatric cardiac surgery varies substantially among centers, but the impact of center-specific effects remains poorly understood.

Objective: To assess the impact of surgical volume and other center effects on early mortality after pediatric cardiac surgery.

Design, Setting, Participants: Retrospective cohort study utilizing risk-adjusted outcome data from the Pediatric Cardiac Care Consortium, a consortium of small and medium size North American centers (<500 cases/year). Hierarchical multivariate logistic regression analysis was used to assess the impact of surgical volume and center effects over time.

Main outcome measure: Risk-adjusted early post-operative mortality.

***Results*:** From 1982 to 2007, 49 centers reported 109,447 operations. Patient characteristics varied significantly among centers. The adjusted odds ratio (OR) for mortality decreased more than 10-fold over the study period (1982 vs. 2007 OR 12.27, 95% CI: 8.52-17.66, p<0.001). Surgical volume was inversely associated with odds of death (additional 100 cases/year OR 0.84, 95% CI: 0.78-0.90, p<0.001). The volume effect was fairly consistent across age groups, risk categories (except the lowest), and time periods. Risk category was the most significant predictor of mortality, while time period, patient age, and a volume-independent center effect had additional weak effects.

***Conclusions*:** Mortality after pediatric cardiac operations has decreased significantly over the last 25 years. RACHS-1 risk category remains the strongest predictor of post-operative mortality. Center-specific variation exists and is only partially explained by

operative volume. Low-risk pediatric cardiac surgery is safely performed at centers performing fewer than 200 cases/year; regionalization or other quality-improvement strategies may be warranted for complex cases.

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INTRODUCTION

Significant progress in pediatric cardiac surgery has raised expectations and generated a need to monitor performance. Despite ongoing debate regarding which metrics should be utilized, operative mortality remains a concrete and important outcome measure frequently used in professional, governmental, and third party-payer databases. In adult cardiac surgery, a correlation between volume and mortality has long been recognized and used to advocate for regionalization.[3, 4] Pediatric cardiac surgical mortality also varies among centers, and in some studies is associated with volume,[1, 5-8] although other factors such as patient characteristics and referral patterns may be involved. For example, studies in England have demonstrated that only a small proportion of the excess mortality at Bristol Royal Infirmary could be attributed to its lower volume.[9] This variation is important to patients, families, physicians, and policymakers.[10, 11] However, the impact of both institutional volume and other center-specific effects on pediatric cardiac post-operative mortality are incompletely understood.

Evaluating institutional performance for pediatric cardiac surgery is difficult for three reasons related to the diversity and complexity of congenital heart diseases (CHDs): first, coding systems do not fully capture the complexity of diagnoses and procedures encountered in pediatric cardiac surgical practice; second, the wide spectrum of risk factors complicates adjustment for case mix; and third, relatively low frequencies of each procedure limit statistical power for detecting differences at an institutional level.[12-14] In

the same example from England, review of the available data demonstrated that single year analysis would have missed the significantly increased mortality in the Bristol Royal Infirmary. [9] Furthermore, ongoing improvements in survival[15, 16] limit the feasibility of increasing power by simply pooling patients over long enrollment periods.

The *Pediatric Cardiac Care Consortium* (PCCC) is a multi-institutional registry collecting patient-level data since 1982 to support quality improvement in CHD surgery.[17] As of the end of 2007, the PCCC included over 137,000 patients from centers with volumes up to 500 operations/year [18]. Detailed information on invasive cardiac procedures, as well as cardiac and non-cardiac diagnoses, permits reliable risk-adjustment. Many previous studies[8, 19-24] have described outcomes after pediatric cardiac operations in childhood, but were limited to specific anomalies, large individual centers of excellence, administrative data, or short time periods; a detailed assessment using clinical outcome data from centers with less than 500 operations per year is lacking. Since a significant number of pediatric cardiac operations are—and will continue to be—performed in centers with less than 500 annual cases, it is important to characterize the factors affecting outcomes in these centers [10, 25, 26]. This need is further supported by previous reports that these centers are more likely to be subject to a volume dependent effect .[1, 10, 25, 26]

Therefore, we set out to characterize the relationship of surgical volume and other risk factors with post-operative mortality at PCCC centers, and determine whether these relationships have changed over time.

METHODS

Data source: the Pediatric Cardiac Care Consortium

The PCCC registry collects detailed clinical data from centers performing pediatric cardiac operations and catheter interventions.[17] All cardiac operations (except isolated ductal ligation in preterm infants under 2.5 kg) are reported prospectively by the centers. Diagnosis and procedure coding takes place at the core facility. Comparison of the case mix at PCCC centers to published datasets reveals a similar distribution of surgical risk categories between PCCC participants and the largest available clinical and administrative datasets even from very large international referral centers (**Figure 1**).[27-36] The University of Minnesota Institutional Review Board has approved the use of this de-identified database for research purposes; informed consent was not required.

For this study, we excluded centers outside North America, one center that transferred patients to outlying hospitals for post-operative recovery at a rate ten-fold higher than the remainder of the database, and any years in which a center contributed incomplete data or performed fewer than 10 operations.

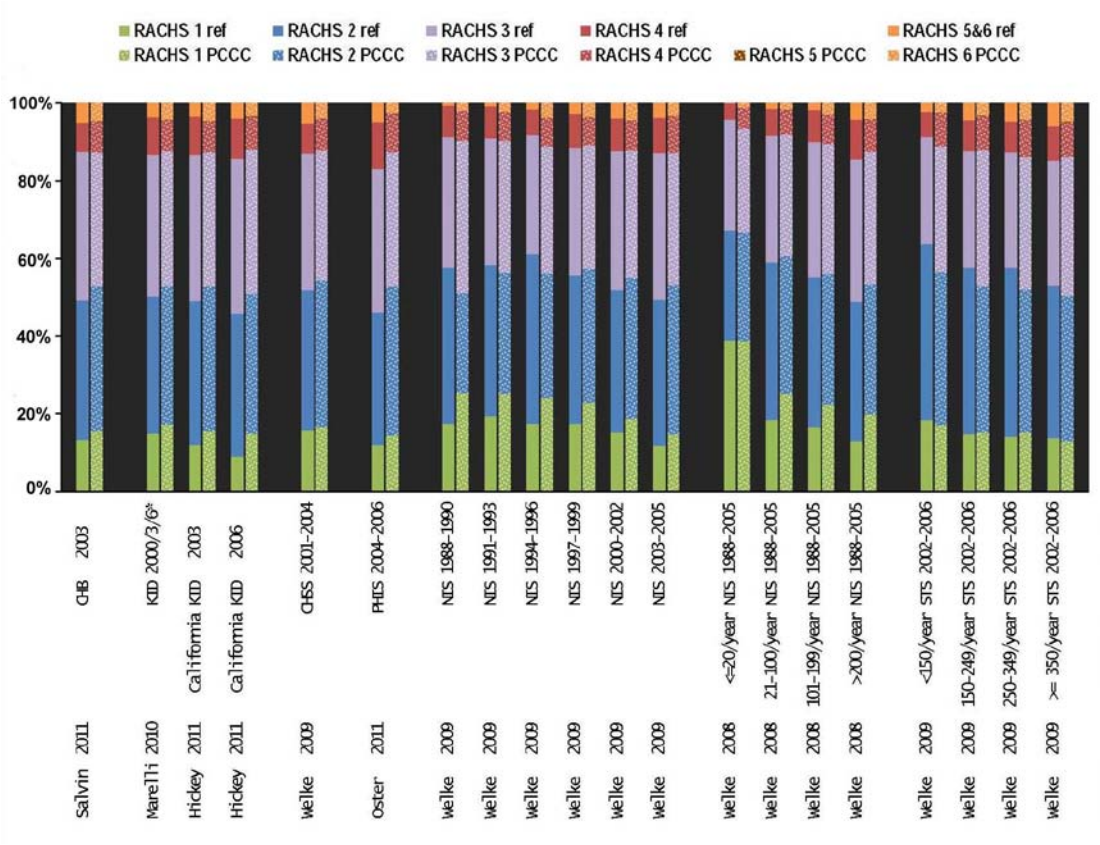

Figure 1. Case mix comparison between PCCC and other datasets reported risk adjusted outcomes. Case mix (distribution by risk category, x-axis) from each reference dataset ("ref", solid colors) and corresponding PCCC subset (speckled colors). Risk categories 5 and 6 are dark and light orange, respectively, or combined as light orange when separate data were unavailable. Datasets (y-axis) are: CHB, Children's Hospital Boston; KID, Kids' Inpatient Database; NIS, Nationwide Inpatient Sample; CHSS, Congenital Heart Surgeons' Society; PHIS, Pediatric Health Information System; STS, Society of Thoracic Surgeons[1]. *The KID includes noncontiguous years: 2000, 2003, and 2006.

Risk adjustment and independent variables

The *Risk Adjusted Classification for Congenital Heart Surgery* system, version 1 (RACHS-1) classifies the congenital cardiac operations into six categories based on expected early mortality rates.[37, 38] Risk category 1 operations have the lowest risk of death, risk category 6 the highest. As category 5 operations are rare, categories 5 and 6

were combined (termed “category 5&6”). Although other risk adjusted methodologies have been described this is the only validated method that has been consistently used among reports describing outcomes for pediatric heart operations.

Other variables available for analysis included patient sex, age at operation (partitioned at 28 days and 1 year), year of operation (with 1982-2007 divided into 5 time periods for most analyses), and center surgical volume (annualized within each time period, modeled as continuous on the logarithmic scale or categorical by tertiles).

Patients, procedures, and outcomes

Surgical volume was calculated using all operations performed for pediatric or adult congenital heart disease. Then, for the multivariate analysis, we excluded adults, hospitalizations ending in transfer to another center, and hospitalizations containing any procedures not classifiable by the RACHS-1 system (expected to be 11-14% of operations).[39, 40] After demonstrating no significant within-patient correlation of outcomes, we included multiple surgical admissions per patient.

Choosing the appropriate endpoint after pediatric cardiac surgery is difficult.[41-45] We used early post-operative mortality, defined as in-hospital death within 30 days of the procedure, as the primary outcome measure. When a single hospital admission involved

multiple operations, we included only one operation, chosen by highest RACHS-1 score[40] first, then by earliest date.

Statistical analysis

Categorical variables were summarized in frequency tables and compared using chi-square tests. Univariable and multivariable mixed-effect logistic regression models were used to compare the association between surgical volume and mortality while adjusting for covariates. Correlation within a center was evaluated by including a random intercept assumed to follow a normal distribution with a mean of 0.

In the multivariable model, we included covariates known or hypothesized to be clinically important or significant at the 10% level in the univariable model. These included era, volume, center, risk category, age group, and sex. Additional models that included interaction terms were analyzed to evaluate the interaction between risk category and era, volume and risk category, volume and era, and volume and age group; each model also included the main effects from the multivariable model.

We report odds ratios (ORs) for death along with the corresponding 95% confidence intervals (CIs). Standard errors and the corresponding t-statistics and p-values for the parameters are computed using the delta method.[46] All tests were two-sided and compared to a cutoff level of 5% without adjustment for multiple comparisons. Timing of death was qualitatively assessed using Kaplan-Meier curves for volume categories

within each risk category.

To assess the relative contribution of each variable to postoperative mortality, we used the likelihood ratio test (LRT) and Akaike information criterion (AIC) in univariable and multivariable models. In the multivariable models, we removed each variable individually and assessed the increase in AIC relative to the full model.[47, 48]

Sensitivity analyses

The proportion of observed deaths minus the mean probability of death predicted by the multivariate model was computed for each center-era combination and plotted against annualized volume to identify outliers; one center with a sharp drop in volume was identified, and models were recomputed after removing the center. Considering that duration of hospitalization before death might vary by center, we repeated the multivariate model with the endpoint of all in-hospital rather than 30-day in-hospital mortality. An analysis using only the first admission per patient was evaluated to compare the results after removing potential intra-patient correlation. To assess the effect of treating age and year as categorical variables, and of annualizing volume, a multivariate model was computed using age and year as continuous variables, and volume based on single years. Finally, we repeated the analysis including procedures unclassifiable by RACHS-1 as a separate category in the regression model.

Analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC). Figures were created using R (R Foundation for Statistical Computing, Vienna, Austria) and Excel (Microsoft, Redmond, WA).

RESULTS

Participating centers and patients

The PCCC registry includes data from 57 participant centers for some or all of the period 1982-2007. These centers performed 118,084 operations on 90,124 patients during 112,030 hospital admissions. After applying exclusion criteria, 49 centers contributed 109,447 operations for volume calculations and 85,023 admissions for multivariate analysis (**Table 1, Figures 2 and 3**). Centers performed 11-534 cases/year overall (mean 173, median 154, standard deviation 99) and 13-458 cases/year grouped by time period (mean 162, median 145, standard deviation 94) (**Figure 4a, b**). Volume was categorized as small (10-99 cases/year), medium (100-199 cases/year), or large (>200 cases/year); standard deviation was rounded to 100 cases/year for continuous-volume analyses. For most variables, cases were not uniformly distributed among volume categories and time periods (**Tables 2 and 3)**; younger patients and higher-risk procedures were more common at larger centers, with the largest discrepancy in risk category 5&6, comprising 1.9%, 2.8%, and 4.4% of cases at small, medium, and large centers respectively ($p<0.001$).

Table 1. Characteristics of hospital admissions.

	Raw[a] dataset		Analysis cohort	
Total	112,003		85,023	
Females	51,539	(46.0%)	39,197	(46.1%)
Males	60,464	(54.0%)	45,826	(53.9%)
Newborns	18,358	(16.4%)	14,986	(17.6%)
Infants	33,643	(30.0%)	28,783	(33.9%)
Children	53,766	(48.0%)	41,254	(48.5%)
Adults	6,235	(5.6%)	--	--
Outcome of hospitalization				
Discharge	103,587	(92.5%)	79,786	(93.8%)
Death	6,806	(6.1%)	5,237	(6.2%)
Transfer	1,610	(1.4%)	--	--
Risk category of highest-risk operation of the hospitalization				
unclassified	13,171	(11.8%)	--	--
1	20,625	(18.4%)	17,935	(21.1%)
2	32,338	(28.9%)	28,389	(33.4%)
3	35,179	(31.4%)	29,434	(34.6%)
4	7,689	(6.9%)	6,563	(7.7%)
5&6	3,001	(2.7%)	2,702	(3.2%)
Operations per admission				
1	106,831	(95.4%)	82,663	(97.2%)
2	4,486	(4.0%)	2,148	(2.5%)
3	565	(0.5%)	185	(0.2%)
4	87	(0.1%)	24	(<0.1%)
5	25	(<0.1%)	3	(<0.1%)
6 or more	9	(<0.1%)		

[a] excluding 28 admissions with missing/inconsistent data

The table presents data from the entire cohort as well as the subgroup used for the multivariable analysis. Data include, total number of admissions, patient's sex and age group, outcome after surgery, *RACHS1* surgical risk category and number of operations per admission.

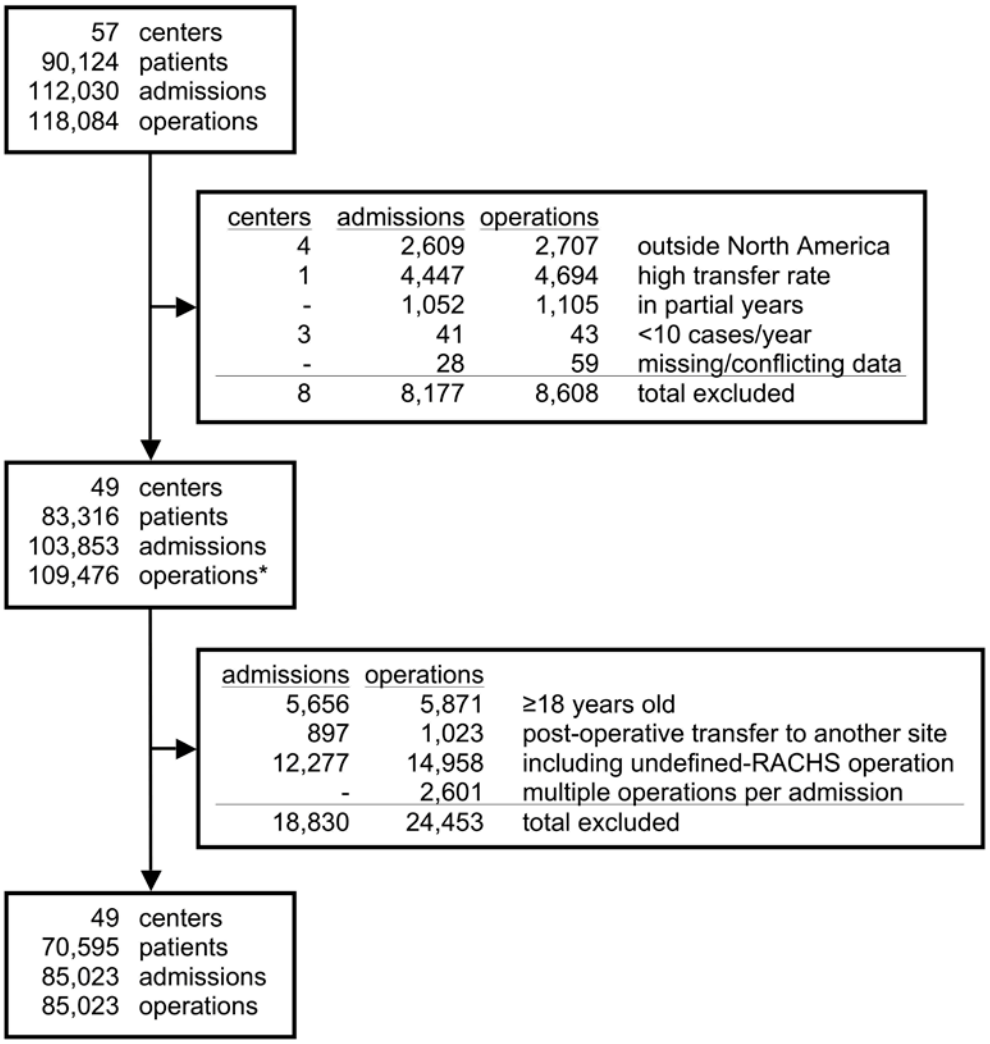

Figure 2. Study flow diagram. The diagram indicates the total number of centers, patients, hospital admissions and cardiac operations within the PCCC. Centers outside North America, centers, centers with less than 10 cases per year, and cases with missing or conflicting data were excluded. In addition, one center in Canada was excluded from the analysis because of a much higher (10x) transfer rate than the other centers. From the remaining cases, we excluded operations in patients older than 18 years of age, patients transferred to another institution, cases with undefined RACHS1 risk category and patients who had multiple operations in the same admission. Note that all eligible operations (*) count towards institutional volume, whereas univariable and multivariable analysis was performed on the final subset of patients after applying the above exclusion criteria.

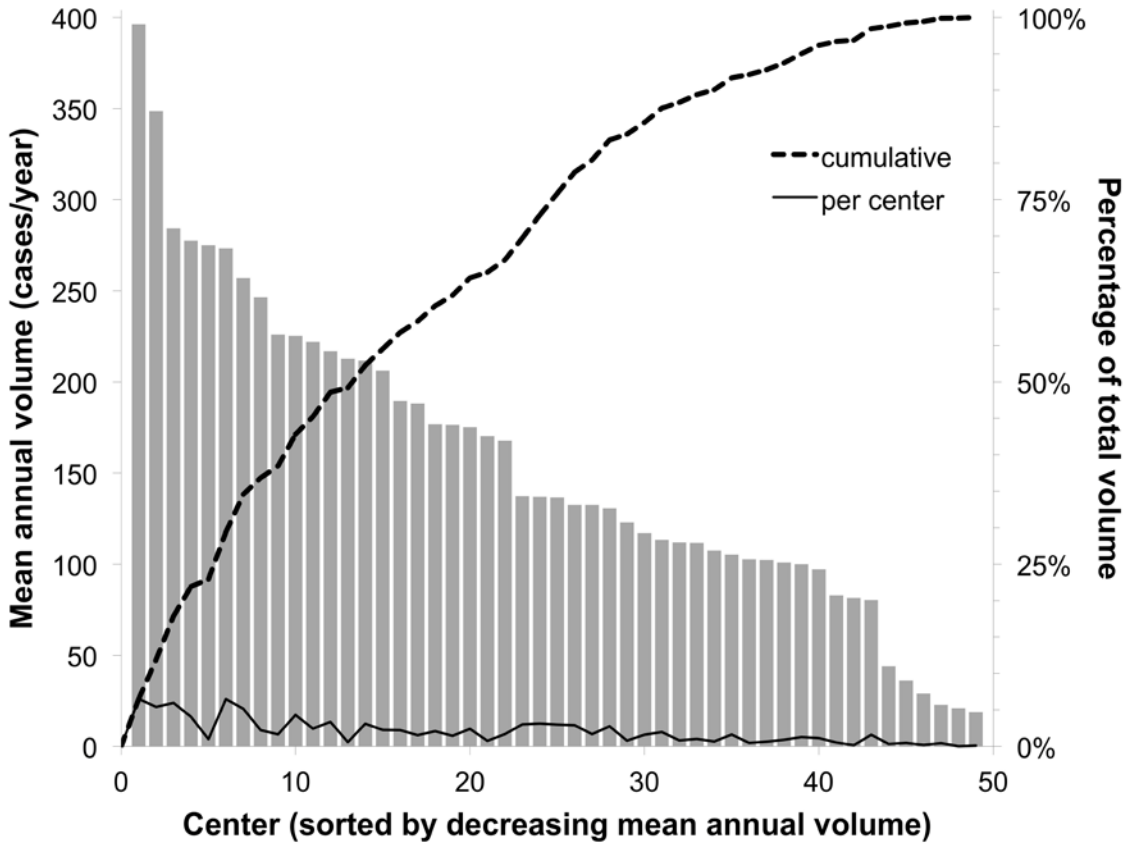

Figure 3. Annual volume and contribution of each center to the cohort. Centers are arranged (x-axis) by mean annual volume (bars, left y-axis) regardless of number of years of participation. The percentage contribution of each center accounts for length of participation and is represented by the solid black line (right y-axis). The dashed line represents the accumulative percentage of patients for all years and centers (right y-axis).

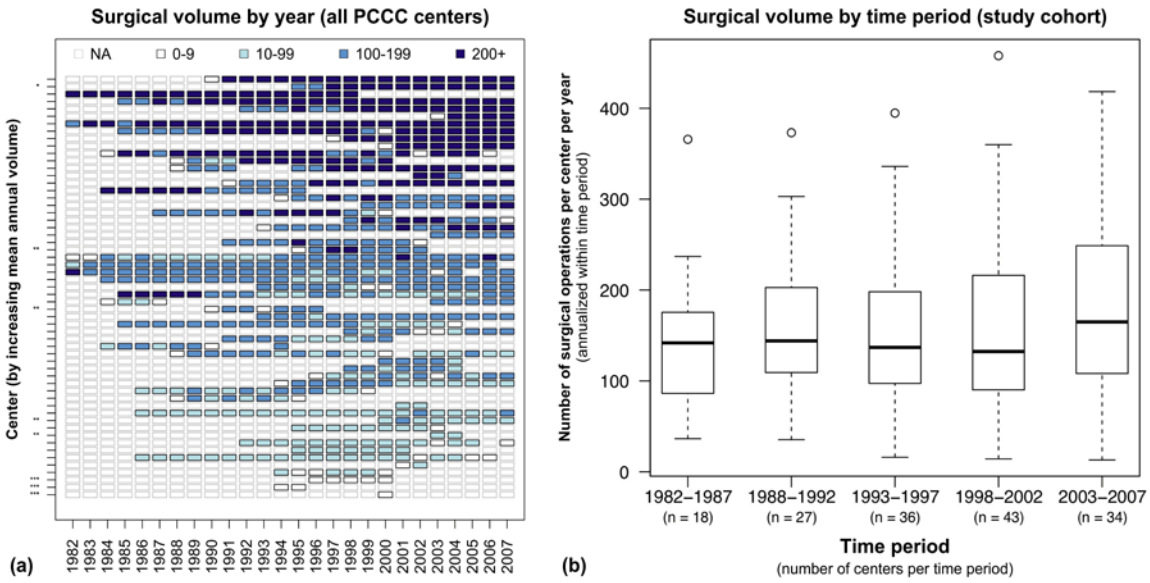

Figure 4. Institutional surgical volumes in the PCCC. (a) Annual center activity (color) for all 57 PCCC centers (y-axis) over time (x-axis). The duration of participation varied among individual centers (NA = center's data not available or incomplete in that year) and 8 centers were excluded (* high transfer rate, ** outside North America, *** <10 cases/year). **(b)** Statistical distribution of the 49 included centers' volumes. The x-axis indicates the years and number of centers in each time period, and the y-axis, surgical volume annualized by time period. Boxes represent median and IQR (interquartile range, 25^{th}-75^{th} percentiles), whiskers represent range within 1.5 x IQR, circles represent values outside 1.5 x IQR.

Table 2. Characteristics of the study cohort by volume category after removing excluded data.

			Volume category (cases/year within time period)					
	All		**Small (10-99)**		**Medium (100-199)**		**Large (>200)**	
Center x TPs	158	(100%)	40	(25.3%)	72	(45.6%)	46	(29.1%)
Operations	85,023	(100%)	7,162	(8.4%)	33,740	(39.7%)	44,121	(51.9%)
Female	39,197	(46.1%)	3,331	[a,b](46.5%)	15,571	[a,c](46.1%)	20,295	[b,c](46.0%)
Male	45,826	(53.9%)	3,831	[a,b](53.5%)	18,169	[a,c](53.9%)	23,826	[b,c](54.0%)
Neonates	14,986	(17.6%)	1,121	(15.7%)	5,894	[c](17.5%)	7,971	[c](18.1%)
Infants	28,783	(33.9%)	2,285	[a](31.9%)	11,111	[a](32.9%)	15,387	(34.9%)
Children	41,254	(48.5%)	3,756	(52.4%)	16,735	(49.6%)	20,763	(47.1%)
Risk category								
1	17,935	(21.1%)	1,822	(25.4%)	7,592	(22.5%)	8,521	(19.3%)
2	28,389	(33.4%)	2,488	[a,b](34.7%)	11,322	[a,c](33.6%)	14,579	[b,c](33.0%)
3	29,434	(34.6%)	2,246	(31.4%)	11,505	(34.1%)	15,683	(35.5%)
4	6,563	(7.7%)	480	[a](6.7%)	2,442	[a](7.2%)	3,641	(8.3%)
5&6	2,702	(3.2%)	126	(1.8%)	879	(2.6%)	1,697	(3.8%)
Outcome								
Discharge	79,786	(93.8%)	6,717	(93.8%)	31,398	(93.1%)	41,671	(94.4%)
Death	5,237	(6.2%)	445	(6.2%)	2,342	(6.9%)	2,450	(5.6%)

The table presents clinical data from the analysis cohort and the distribution of surgical cases by volume category. Data include, total number of admissions, patient's sex and age group, *RACHS1* surgical risk category and outcome after surgery.

Table 3. Characteristics of the study cohort by time period after removing excluding data

		Time Period: years				
	All	**1: 1982-1987**	**2: 1988-1992**	**3: 1993-1997**	**4: 1998-2002**	**5: 2003-2007**
Center x TPs	158 (100%)	18 (11.4%)	27 (17.1%)	36 (22.8%)	43 (27.2%)	34 (21.5%)
Patients	85,023 (100%)	8,162(9.6%)	13,600(16%)	19,818(23.3%)	22,279(26.2%)	21,164(24.9%)
Female	39,197 (46.1%)	3,775 (46.3%) [a,b,c,d]	6,331 (46.6%) [a,e,f,g]	9,319 (47.0%) [b,e,h]	10,274 (46.1%) [c,f,h,j]	9,498 (44.9%) [d,g,j]
Male	45,826 (53.9%)	4,387 (53.7%) [a,b,c,d]	7,269 (53.4%) [a,e,f,g]	10,499 (53.0%) [b,e,h]	12,005 (53.9%) [c,f,h,j]	11,666 (55.1%) [d,g,j]
Neonates	14,986 (17.6%)	1,018 (12.5%)	2,165 (15.9%)[e]	3,407 (17.2%)[e]	4,190 (18.8%)[j]	4,206 (19.9%) [j]
Infants	28,783 (33.9%)	2,214 (27.1%)[a]	3,956 (29.1%)[a]	6,286 (31.7%)	7,899 (35.5%)	8,428 (39.8%)
Children	41,254 (48.5%)	4,930 (60.4%)	7,479 (55%)	10,125 (51.1%)	10,190 (45.7%)	8,530 (40.3%)
Risk category						
1	17,935 (21.1%)	1,999 (24.5%)[a,b]	3,421 (25.2%) [a,e]	4,827 (24.4%)[b,e]	4,509 (20.2%)	3,179 (15%)
2	28,389 (33.4%)	2,180 (26.7%)[a]	3,793 (27.9%)[a]	6,441(32.5%)	7,990 (35.9%)	7,985 (37.7%)
3	29,434 (34.6%)	3,334 (40.8%)	5,078 (37.3%)	6,385 (32.2%)[h]	7,231(32.5%)[h]	7,406 (35%)
4	6,563 (7.7%)	547 (6.7%)[a,b,c]	1,013 (7.4%)[a,e,f]	1,446 (7.3%)[b,e,h]	1,651 (7.4%)[c,f,h]	1,906 (9%)
5&6	2,702 (3.2%)	102 (1.2%)	295(2.2%)	719 (3.6%)[h,i]	898 (4%)[h]	688 (3.3%)[i]
Outcome						
Discharge	79,786 (93.8%)	7,341 (89.9%)	12,467(91.7%)	18,394(92.8%)	21,135(94.9%)	20,449(96.6%)
Death	5,237(6.2%)	821(10.1%)	1,133(8.3%)	1,424(7.2%)	1,144(5.1%)	715(3.4%)

Proportion of each variable differs significantly (Bonferroni-corrected p<0.0006) between time periods except as indicated: [a, b, c, d, e, f, g, h, i] no pairwise difference between TPs 1&2, 1&3, 1&4, 1&5, 2&3, 2&4, 2&5, 3&4, 3&5, 4&5 respectively. TP, time period. Time periods: (1) 1982-1987, (2) 1988-1992, [2] 1993-1997, (4) 1998-2002, (5) 2003-2007. The product Center X TPs indicates the number of centers multiplied by the number of time periods that they contributed data to the registry. The table displays clinical data from the analysis cohort and the distribution of operations by surgical era. Data include, total number of admissions, patient's sex and age group, *RACHS1* surgical risk category and outcome after surgery.

Unadjusted Outcomes

Table 4 shows the distribution of admissions and deaths by risk category for the whole study period and in the most recent era (unadjusted mortality 5.2% overall, 2.3% for 2003-2007). Mortality varied widely across time periods and risk categories but generally decreased throughout the study period, except in the lowest risk category where it has remained low and stable since the late 1980's (**Figure 5a**).

Table 4. Raw data by risk category, overall and for the most recent era.

Risk	Entire study period (1982–2007)			Time period 5 (2003–2007)		
category	**Admissions**	**Deaths**	**Mortality**	**Admissions**	**Deaths**	**Mortality**
1	17935 (21.1%)	99 (2.2%)	0.6%	3179 (15.0%)	14 (2.9%)	0.5%
2	28389 (33.4%)	555 (12.6%)	2.0%	7985 (37.7%)	56 (11.6%)	0.7%
3	29434 (34.6%)	1892 (42.9%)	6.4%	7406 (35.0%)	197 (40.6%)	2.7%
4	6563 (7.7%)	951 (21.5%)	14.5%	1906 (9.0%)	115 (23.7%)	6.0%
5&6	2702 (3.2%)	918 (20.8%)	34.0%	688 (3.3%)	103 (21.2%)	15.0%
Total	85023	4415	5.2%	21164	485	2.3%

Deaths reported by risk category for the entire study period and for the most recent time period between 20003 and 2007. The table displays the number of deaths and mortality rate for each risk category and the contribution of each category's deaths towards the overall deaths reported in the registry.

Kaplan-Meier survival curves for volume categories, stratified by risk categories (**Figure 6**), demonstrate overall lower mortality at large compared to small and medium centers ($p<0.001$) except in risk category 1. Most of the separation occurs within one day of the operation; the survival curves are approximately parallel thereafter. The initial drop in survival appears more prominent at small than medium centers, but the difference is not statistically significant.

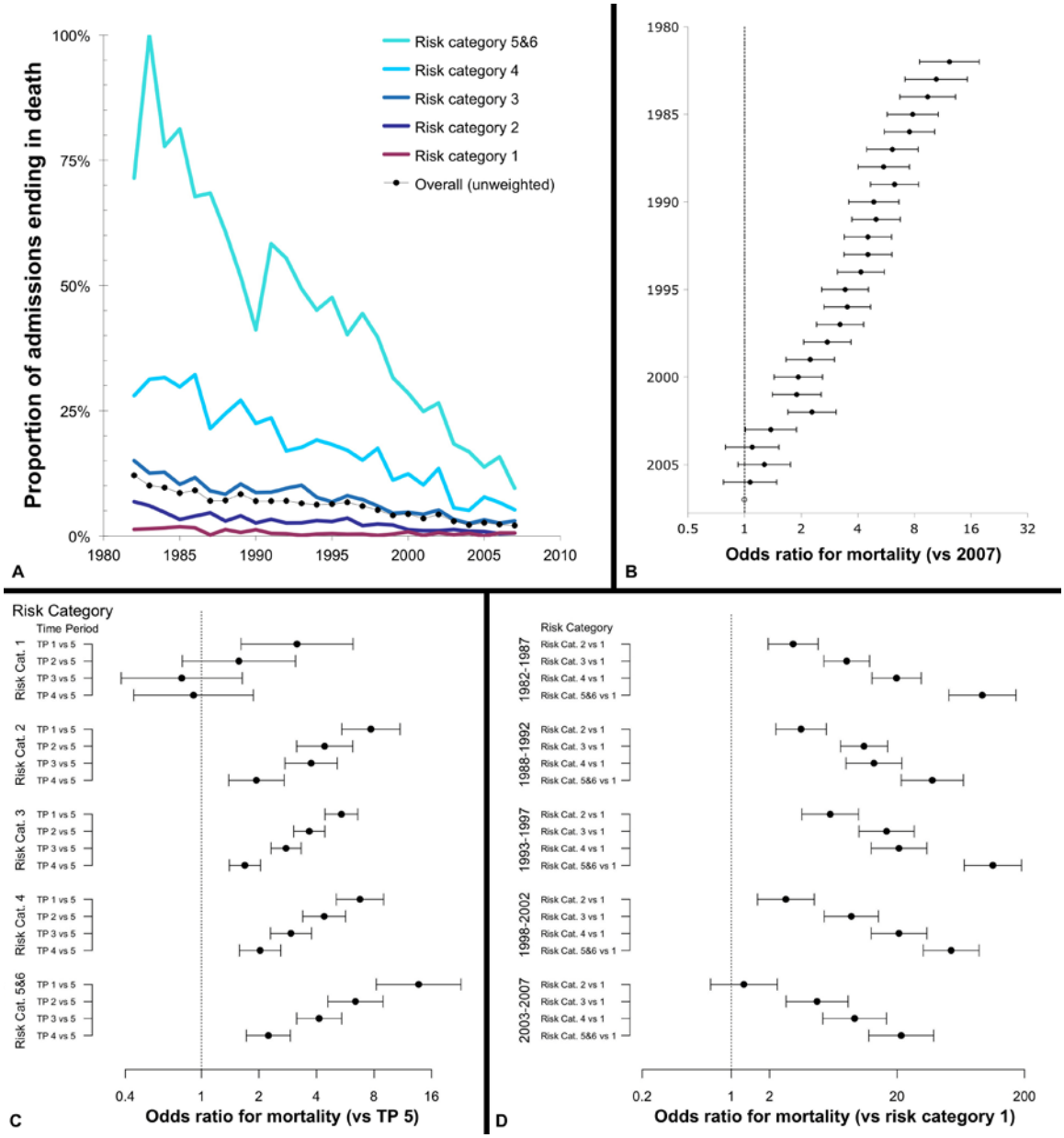

Figure 5. Mortality by time and risk category. (a) Unadjusted mortality over time, for the overall cohort and by risk category. **(b)** Risk-adjusted mortality over time, shown as ORs (circles) and 95% CIs (whiskers) (reference: year 2007). **(c)** Adjusted mortality across time periods, by risk category (reference: time period 5). **(d)** Adjusted mortality across risk categories, by time period (reference: risk category 1).

Time periods: (1) 1982-1987, (2) 1988-1992, (3) 1993-1997, (4) 1998-2002, (5) 2003-2007

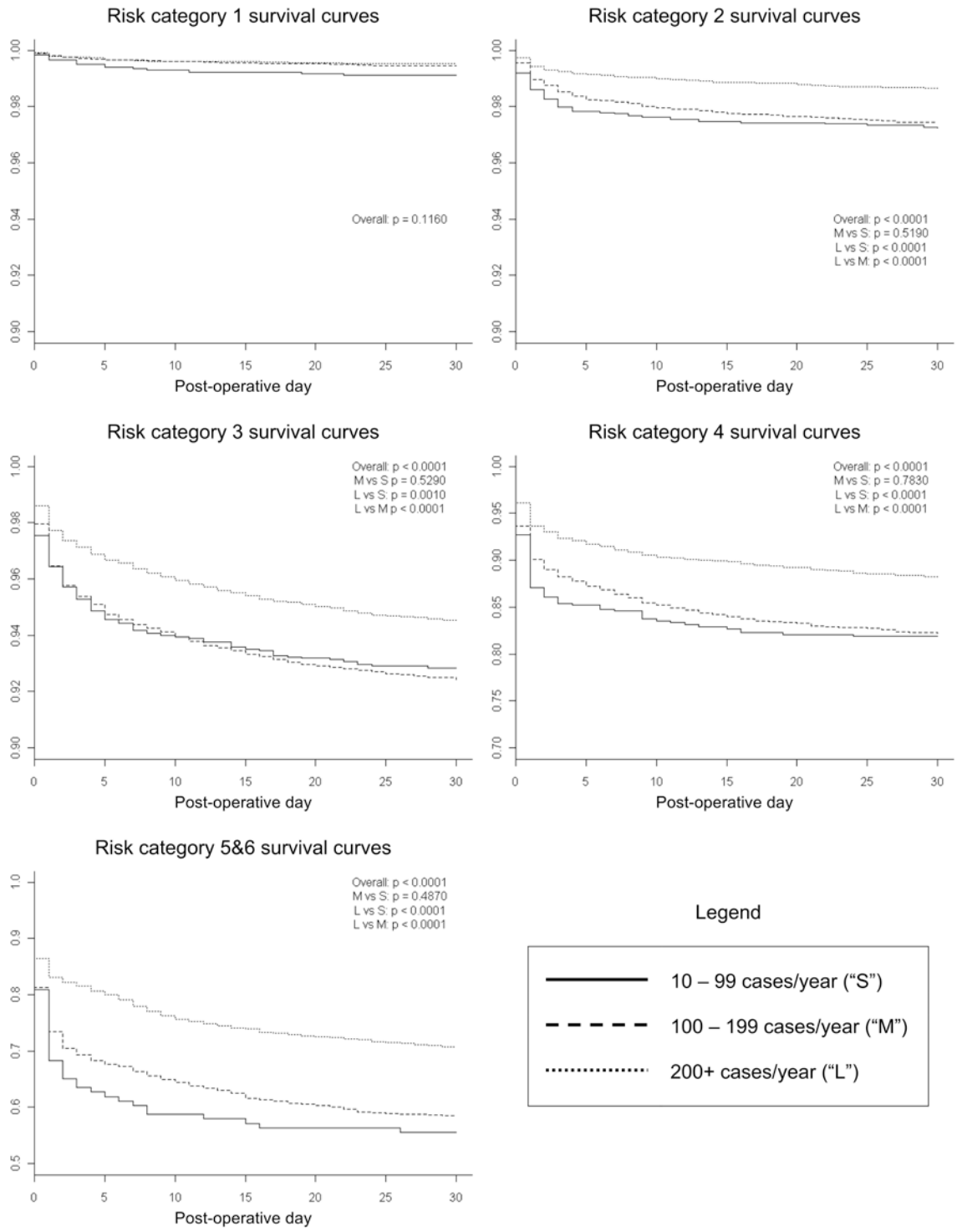

Figure 6. Kaplan-Meier (KM) survival curves for volume categories by risk category. The y-axis indicates fraction of patients surviving on each post-operative day, and is scaled differently on each plot. P-values were calculated by log-rank test without adjustment for multiple comparisons. "S": small, "M": mid-sized, "L": large.

Univariable and multivariable analysis

Mortality decreases with increased surgical volume

Institutional volume was significant in both univariable and multivariable analysis for the main effects, although less important than other variables. Overall, volume was inversely correlated with mortality: OR for death was 0.72 by univariable analysis, 95% CI: 0.67-0.77, p<0.001 and 0.84 by multivariable analysis (full model), 95% CI: 0.78-0.90, p<0.001 (OR given per additional 100 operations/year with volume used as continuous

Table 5. Univariable and multivariable associations of potential factors.

	Univariable analysis			Multivariable analysis		
	OR	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
Volume (per 100 cases/year)	0.72	(0.67-0.77)	<0.001	0.84	(0.78-0.90)	<0.001
Risk category 5&6 vs. 1	111.9	(89.8-139.6)	<0.001	67.0	(53.1-84.5)	<0.001
Risk category 4 vs. 1	33.3	(26.9-41.4)	<0.001	23.1	(18.5-28.8)	<0.001
Risk category 3 vs. 1	13.1	(10.6-16.1)	<0.001	10.1	(8.2-12.5)	<0.001
Risk category 2 vs. 1	3.9	(3.1-4.8)	<0.001	3.4	(2.7-4.2)	<0.001
Neonates vs. children	8.5	(7.8-9.3)	<0.001	3.3	(3.0-3.6)	<0.001
Infants vs. children	2.5	(2.3-2.8)	<0.001	2.3	(2.1-2.5)	<0.001
Neonates vs. infants	3.4	(3.1-3.6)	<0.001	1.4	(1.33-1.6)	<0.001
Time Period 1 vs. 5	4.4	(3.8-5.0)	<0.001	6.5	(5.6-7.6)	<0.001
Time Period 2 vs. 5	3.3	(2.9-3.7)	<0.001	4.2	(3.7-4.8)	<0.001
Time Period 3 vs. 5	2.7	(2.4-3.0)	<0.001	3.1	(2.7-3.5)	<0.001
Time Period 4 vs. 5	1.8	(1.6-2.0)	<0.001	1.9	(1.7-2.1)	<0.001
Females vs. males	0.98	(0.92-1.04)	0.50	1.20	(1.13-1.29)	<0.001

Results of the univariable and multivariable analysis examining main effects of center volume changes (expressed as 100 cases/year), *RACHS1* risk category, age group, time period and patient's sex. In both analyses, center's annual surgical volume is analyzed as continuous variable. Time periods: (1) 1982-1987, (2) 1988-1992, (3) 1993-1997, (4) 1998-2002, (5) 2003-2007.

variable) (**Tables 5 and 6**). Multivariable analysis with modeling for interaction terms revealed that the volume-mortality relationship persisted across age groups, risk categories, and time periods with some variation. Of note, volume had no effect in risk category 1 (OR 0.99, 95% CI: 0.79-1.25) (**Table 6**). Logistic regression analysis for interaction reveals that volume interacts with risk category (p=0·0049) and time period (p=0·0023), but no interaction with age (p=0·3494).

Table 6. The volume-mortality relationship.

	OR	95% CI	p value
Overall 100 case/year increase[a]	0.84	(0.78-0.9)	<0.001
Risk category by volume interaction (p=0·0049)			
100 case/year increase – risk category 1	0.98	(0.78-1.23)	0.86
100 case/year increase – risk category 2	0.74	(0.66-0.83)	<0.001
100 case/year increase – risk category 3	0.89	(0.82-0.97)	0.006
100 case/year increase – risk category 4	0.85	(0.77-0.93)	0.001
100 case/year increase – risk category 5&6	0.77	(0.69-0.86)	<0.001
Time period by volume interaction (p=0·0023)			
100 case/year increase – 1982-1987	0.83	(0.73-0.95)	0.006
100 case/year increase – 1988-1992	0.77	(0.69-0.87)	<0.001
100 case/year increase – 1993-1997	0.77	(0.70-0.85)	<0.001
100 case/year increase – 1998-2002	0.93	(0.85-1.01)	0.10
100 case/year increase – 2003-2007	0.78	(0.69-0.88)	<0.001
Age group by volume interaction ((p=0·3494)			
100 case/year increase – neonates	0.86	(0.79-0.93)	<0.001
100 case/year increase – infants	0.84	(0.77-0.92)	<0.001
100 case/year increase – children	0.80	(0.72-0.88)	<0.001

[a] Values are derived from four separate models (main effect model and three interaction models), each controlling for correlation within center but not within patient.

Results of the analysis examining interaction terms between center volume changes (expressed as 100 cases/year) and each of the subsequent covariates separately: risk category, time period and age group.

Mortality varies by center

Individual center effects, representing the deviation from overall adjusted odds of death, varied significantly even after adjustment for patient factors (**Figure 7a and b**). Center specific variation was evaluated by including a random intercept, which represents the overall effect of all omitted center-specific covariates that cause the deviation of a center from the overall adjusted odds of death.

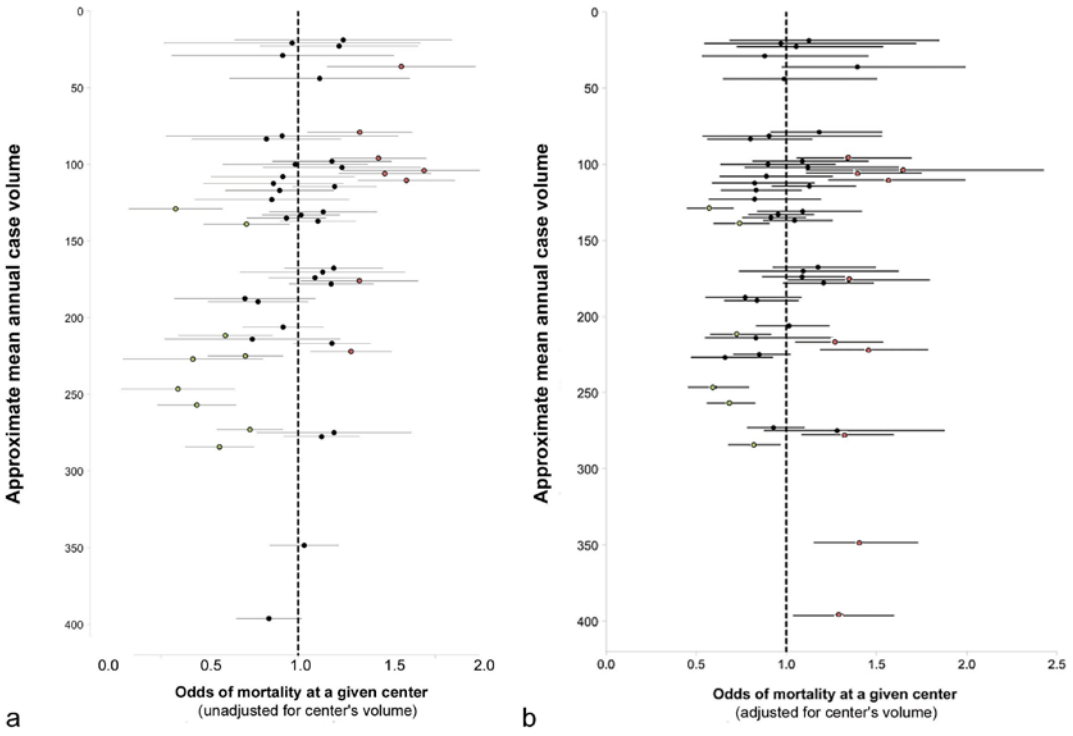

Figure 7. Relative odds of post-operative mortality in the 49 PCCC centers. The odds of death are the results of the multivariable analysis for the main effects model and application of random intercept for accounting for center's variation. (a) Centers are arranged by mean annual case volume and results are adjusted for risk category, time period, age group and sex. Center specific variation exists with higher postoperative risk of death existing more frequently in smaller and medium centers. (b) Centers are similarly arranged as in graph (a) and results are adjusted for the same variables including center's case volume within a time period. The pattern of increased postoperative mortality in smaller and medium size centers disappears after adjustment for volume. For some centers, volume was adjusted slightly up or down to prevent overlap in the figure; this did not change the order of centers or alter any center's volume by more than 2 cases/year. Green and red dots indicate an odds ratio significant less or above the group's average taken as 1.

Overall, 8 out of 49 (16%) centers have a significantly increased risk adjusted OR for postoperative mortality, 9 (18 %) have decreased OR, while 32 centers (64%) behave in non-significant manner compared to the average center. From the small or medium centers (n=34) with less than 200 cases a year 7 centers (20%) have higher postoperative mortality than the risk adjusted average, 25 centers (73.5%) have average outcomes and only 2 (6%) have decreased postoperative mortality. From the large centers (n=15) with more than 200 annual cases, 7/15 (47%) have better outcomes than the expected risk adjusted average, 7/15 match the average and only 1/15 (6.6%) have higher than expected postoperative mortality. After adjustment for volume this pattern disappears (**Figure 7b**). More specifically, from the small and medium size centers there are 2 (6%) centers with increased mortality, 2 (6%) with decreased mortality and 30 (88%) with average mortality, while the large centers are equally split between low, average and high performers with 5 centers in each category (**Table 7**).

Table 7. Distribution of centers according to their performance and volume category.

	Small & medium centers (<200 cases/year)		**Large centers (>200 cases per year)**		**All centers**	
	unadjusted	**adjusted**	**unadjusted**	**adjusted**	**unadjusted**	**adjusted**
Low	**7**	**2**	**7**	**5**	**8**	**7**
Average	**25**	**30**	**7**	**5**	**32**	**35**
High	**2**	**2**	**1**	**5**	**9**	**7**
Total	**34**		**15**		**49**	

Centers are classified as low, average and high performers based on their postsurgical risk adjusted mortality compared to the group's average. Small and medium size centers are more frequently underperforming compared to the group's average. This pattern disappears after adjustment for volume.

Center-specific variation remained significant even after controlling for volume ($p<0.001$ by LRT) (**Table 8**). The center effect assumed a normal distribution with a mean of 0 and standard deviation of 0.29 (95% CI: 0.21-0.37, $p<0.001$). The inclusion of volume in the multivariate model reduced the variability of the center effect by 20%. These findings demonstrate the importance of center-specific effects independent of institutional volume.

Table 8. Significance of each variable included in the final model.

Variable	Degrees of freedom	Univariable		Multivariable	
		LRT	**AIC**	**LRT**	**AIC**
Sex	1	419	34302	31	27529
Risk category	4	5648	29079	3137	30629
Age group	2	3309	31414	676	28172
Time period	4	1020	33707	768	28260
Surgical volume	1	505	34216	25	27523
Center effect	1	419	34300	181	27679
All variables	0			0	27500

LRT, likelihood ratio test; AIC, Akaike information criterion. For univariable analyses, the LRT is used to compare the intercept-only model (AIC 34300) with the corresponding univariable model; lower AIC indicates that the model fits the data better. For the multivariate analysis, the LRT is used to compare the full model including all variables (AIC 27500) with a model omitting one variable at a time; here, higher AIC indicates the removed variable fits the data better. For both models, higher LRT indicates a more significant impact of a variable. Center effect was evaluated by including a random intercept with 1 df.

Sensitivity analyses

We performed multiple sensitivity analyses to assess the stability of our results. We found no important differences in analyses that included only the first admission per patient, included cases with undefined RACHS-1 risk category, used the endpoint of all

in-hospital mortality, excluded outliers, or treated year and age as continuous variables and did not annualize volume.

DISCUSSION

Using multi-institutional data collected prospectively over 25 years of pediatric cardiac surgery, we analyzed trends in post-operative mortality and quantified the influence of risk factors including institutional volume. Overall, survival after pediatric cardiac surgery improved substantially, consistent with a previous, smaller study.[14] The decrease in mortality occurred across all age and risk groups except the minimal risk category 1, which has reached a plateau. Over time, the gaps between the different risk categories narrowed, but RACHS-1 score remains by far the best predictor of post-operative mortality.[49] There is residual age- and sex-specific risk that is not captured by RACHS-1, with younger age and female sex associated with increased risk of death.

Volume as a risk factor for pediatric cardiac surgical mortality

We demonstrated a statistically significant protective effect of increased surgical volume on post-operative mortality. The effect was clinically relevant (relative odds reductions generally 10-30%, similar to a previous report[9]) but modest compared to other variables. Other authors have found that the volume-mortality relationship varies substantially by

patient age[23, 50] and may be attenuated[26, 51] or even absent[52] in the modern era; our analysis did not corroborate either finding.

Previous reports suggest the presence of a critical threshold for surgical volume (variously 75-300 cases/year). We did not identify such a threshold within the range of volumes available in the PCCC registry, although it is possible that one exists outside this range (i.e. with optimal outcomes at extremely large centers). Regardless, a substantial fraction of patients do not have easy access to these highly specialized centers. To assess the relevance of this issue, we sought to estimate the relative sizes of the PCCC and non-PCCC patient populations. In 2003, 122 United States (US) centers performed about 25,000 pediatric cardiac operations by one report;[53] Jacobs has estimated a range of 18,000-33,000 cases/year,[54] and Chang et al suggested 19,000 cases/year.[11] By comparison, 34 US centers submitted 5,323 cases to the PCCC for 2003 (i.e. 15-30% of the estimated national total). Alternatively, comparing PCCC infantile repairs of truncus arteriosus, tetralogy of Fallot, and complete transposition to US birth defect data[55] suggests that US-based PCCC centers represented between 10-20% of the 2004-2006 national total (data not shown). The overall distribution of volume at US centers is unknown, but we estimate that centers similar to those participating in the PCCC (<500 cases/year) might perform about 50% of the pediatric cardiac operations in the US. This underscores the importance of understanding and improving outcomes from such centers.

Effect of volume by risk category

The volume-mortality relationship varied significantly by risk category. The complete absence of effect for the lowest risk category suggests that operations in this category are safely performed at smaller centers, consistent with most previous reports.[1, 50, 56] We speculate that these operations have such small risk (unadjusted mortality 0.5% in the modern era) that mortality is independent of institutional experience. Even for higher-risk operations, the absolute effect of volume is relatively modest at current mortality rates.

Limitations of volume as a quality indicator

Institutional surgical volume has been proposed as a quality indicator for pediatric cardiac surgery.[53] However, our study found that volume is a weak predictor of a center's mortality rate and explains only a fraction of institutional variability, similar to previous reports from other databases.[1, 7, 8, 51] Our data is consistent with other studies[1, 6, 7, 24] suggesting that volume should not be used in isolation to predict quality at the level of individual institutions or surgeons.

Regionalization has been considered for pediatric cardiac surgery;[57] this is a complex policy issue, but if undertaken, our results suggest centers should be targeted by direct analysis of quality rather than by volume alone. Implications for selective referral

strategies[19, 25] are similar; our study provides reference data useful for identifying patient subgroups where such strategies have the greatest potential benefit.

Strengths and limitations

Strengths of our study include the large data set, ability to characterize changes over time, use of clinical rather than administrative data,[6] and attention to recommendations regarding statistical approach to volume-outcome analysis.[47, 48, 58, 59]

Limitations are mainly those typical of retrospective registry-based studies; we did not control for all patient factors, such as prematurity, weight, comorbidities, and socio-demographic variables, and institutional factors, such as team composition, transfusion practices, infection control, and care pathways,[56, 60-64] that may affect outcomes. We grouped operations by RACHS-1 risk category, and therefore cannot evaluate whether our results apply uniformly to all operations in a given risk category. The behavior of specific operations will be the subject of a future detailed investigation. The voluntary and changing makeup of the PCCC may limit our inference, and with only a few centers performing over 350 operations/year, this study cannot assess whether the volume-mortality relationship strengthens, persists, or is attenuated, at very large, specialized centers. However, one prior study including multiple large centers from the Society of Thoracic Surgeons congenital heart disease database suggested that the volume-mortality effect is essentially limited to centers below 300 operations/year.[1] Finally, unmeasured

referral patterns may confound the results of any observational volume-outcome analysis,[12, 65] in which case volume and mortality would indeed be correlated, but not causally related.

Future research

Studies of volume-outcome relationships set the stage for investigation of which factors mediate these relationships, and for targeted quality improvement.[1, 38, 66] However, improvement efforts using mortality as the endpoint are hampered by limited statistical power.[67] Future research will need to identify alternative endpoints that can support rapid-cycle quality improvement while also incorporating other outcomes of increasingly recognized importance such as non-fatal complications, reoperation, neurologic and other non-cardiac morbidity, and cost-effectiveness.

Conclusions

In this large longitudinal multi-institutional registry, mortality after pediatric cardiac surgery has declined substantially over the past 25 years. Mortality remains an important endpoint for higher-risk operations, but new endpoints should be developed and validated across the spectrum of pediatric cardiac operations. Center-specific variation exists even after risk-adjustment, suggesting some of the post-operative mortality is preventable, but institutional volume only partially explains this variation. Lowest-risk pediatric cardiac

operations can be safely performed at centers with fewer than 200 annual operations, whereas additional research is needed to identify strategies for reducing preventable mortality after medium- and high-risk operations.

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