

# **SUPPLEMENTAL MATERIAL**

## **Data S1.**

### **Supplemental Methods**

#### **Model 2**

Proportional hazard assumptions were checked by comparing the log-log curve versus log-time. Variables included in the multivariable model were age at surgery, sex, prematurity, diagnosis (hypoplastic left heart syndrome [HLHS] vs other anatomies), shunt type, surgical times (cardiopulmonary bypass [CPB] time, aortic clamp time, deep hypothermic cardiac arrest [DHCA] time), and ECMO use in the first 28 PODs. A backward conditional strategy was used for entry and retention of variables in the multivariable model. A candidate variable was retained in the model if the P value was  $<0.05$ . Age and weight were tested for correlation using Spearman's Rho test according to their non-parametric distribution. Since a significant correlation was proven, only age was included in the model. Results were expressed in terms of hazard ratios and 95% CIs.

#### **Model 3**

Each element of care (MMVR, opioid TDD and daily FB) was modeled over time using log-normal distribution (for MMVR and opioid TDD) or normal distribution (FB). Center affiliation was tested as the main predictor of the element trajectory over time, keeping the other variables constant. A first model included a fixed effect for center affiliation, time (days from surgery), interaction center\*time, and random effect for subjects. A subsequent multivariable model was finally developed for each element of care adjusting for age, diagnosis, shunt type, surgical times and ECMO support (yes/no). All results were scaled to mean changes in the elements of care and

95% CIs. Model fit was checked using residual plots. All statistical analyses were performed using IBM SPSS (version 25.0, IBM Corp. Armonk, New York, U.S.A.) and R (version 3.6.2., R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

## Supplemental Results

### Estimating equations for unadjusted models:

$$\widehat{MMVR}_i = e^{\Lambda}(3.04 + 0.36 * Center2_i + 0.16 * Center3_i - 0.27 * Center4_i + 0.07 * Center5_i - 0.09 * Time_i - 0.01 * Center2_i * Time_i - 0.11 * Center3_i * Time_i - 0.40 * Center4_i * Time_i - 0.10 * Center5_i * Time_i + b_i + \varepsilon_i)$$

$$\widehat{TTD}_i = e^{\Lambda}(1.96 - 0.88 * Center2_i - 0.28 * Center3_i - 2.02 * Center4_i - 1.12 * Center5_i - 0.15 * Time_i + 0.05 * Center2_i * Time_i - 0.02 * Center3_i * Time_i + 0.07 * Center4_i * Time_i + 0.07 * Center5_i * Time_i + b_i + \varepsilon_i)$$

$$\widehat{FB}_i = -8.66 + 20.62 * Center2_i + 21.40 * Center3_i + 70.57 * Center4_i + 15.86 * Center5_i + 1.27 * Time_i - 0.68 * Center2_i * Time_i - 0.34 * Center3_i * Time_i - 2.63 * Center4_i * Time_i - 0.12 * Center5_i * Time_i + b_i + \varepsilon_i$$

### Estimating equations for adjusted models:

$$\widehat{MMVR}_i = e^{\Lambda}(3.09 + 0.31 * Center2_i + 0.11 * Center3_i - 0.35 * Center4_i + 0.07 * Center5_i - 0.09 * Time_i - 0.004 * Center2_i * Time_i - 0.11 * Center3_i * Time_i - 0.40 * Center4_i * Time_i - 0.10 * Center5_i * Time_i - 0.0004 * Age_i + 0.001 * CPBtime_i + 0.003 * DHCAtime_i - 0.002 ACctime_i + 0.005 * HLHS_i - 0.19 * SanoShunt_i + 0.02 * ECMO_i + b_i + \varepsilon_i)$$

$$\widehat{TTD}_i = e^{\Lambda}(0.82 - 1.19 * Center2_i - 0.12 * Center3_i - 1.35 * Center4_i - 0.60 * Center5_i - 0.09 * Time_i + 0.003 * Center2_i * Time_i - 0.06 * Center3_i * Time_i + 0.01 * Center4_i * Time_i + 0.03 * Center5_i * Time_i + 0.004 * Age_i + 0.005 * CPBtime_i + 0.008 * DHCAtime_i - 0.006 * ACctime_i + 0.98 * HLHS_i + 0.12 * SanoShunt_i + 0.89 * ECMO_i + b_i + \varepsilon_i)$$

$$\widehat{FB}_i = -4.68 + 20.40 * Center2_i + 20.99 * Center3_i + 67.16 * Center4_i + 16.01 * Center5_i + 1.26 * Time_i - 0.68 * Center2_i * Time_i - 0.34 * Center3_i * Time_i - 2.63 * Center4_i * Time_i - 0.11 * Center5_i * Time_i - 0.004 * Age_i - 0.04 * CPBtime_i + 0.001 * DHCAtime_i + 0.006 ACctime_i + 0.75 * SanoShunt_i + 2.66 * HLHS_i + 0.14 * ECMO_i + b_i + \varepsilon_i$$

**Table S1. Pairwise comparisons of Centers by ANOVA-rank analysis (Table 1).**

Variable	Centers									
	1-2	1-3	1-4	1-5	2-3	2-4	2-5	3-4	3-5	4-5
Age at surgery	0.002	1.000	1.000	0.032	0.012	0.005	0.656	1.000	0.346	0.139
Gestational age	0.046	0.003	0.007	1.000	1.000	1.000	0.641	1.000	0.393	0.419
CPB time	1.000	1.000	<0.001	0.197	1.000	<0.001	1.000	<0.001	0.188	<0.001
DHCA time	<0.001	<0.001	<0.001	1.000	0.005	<0.001	<0.001	<0.001	0.011	<0.001
Aortic clamp time	<0.001	<0.001	<0.001	0.696	1.000	0.067	<0.001	<0.001	<0.001	<0.001
CICU length of stay	<0.001	<0.001	0.001	0.005	<0.001	<0.001	0.323	1.000	<0.001	<0.001
Hospital length of stay	1.000	0.219	<0.001	<0.001	1.000	0.010	0.009	0.089	<0.001	<0.001
Duration of mandatory ventilation	1.000	<0.001	<0.001	<0.001	0.001	<0.001	0.004	<0.001	1.000	<0.001
Median MVR per day per patient	0.002	<0.001	<0.001	0.069	1.000	<0.001	0.492	<0.001	0.131	<0.001
Daily fluid balance per kg per patient	0.045	<0.001	<0.001	<0.001	0.178	<0.001	1.000	<0.001	0.185	<0.001
Daily fluid intake per kg per patient	0.016	<0.001	1.000	1.000	1.000	0.027	0.008	0.001	<0.001	1.000
Daily fluid output per kg per patient	1.000	0.390	<0.001	0.004	0.086	<0.001	0.003	<0.001	1.000	<0.001
Duration of opioid administration	1.000	0.694	<0.001	0.350	1.000	<0.001	1.000	<0.001	1.000	<0.001
Opioid total daily dose per patient	0.845	0.001	<0.001	0.316	0.001	<0.001	0.046	1.000	1.000	0.186

P values are adjusted p values by Bonferroni-Dunn correction for multiple tests. Significance level is set at two-sided p value <0.05. CBP: cardiopulmonary by-pass; CICU: cardiac intensive care unit; DHCA: deep hypothermic circulatory arrest; MMVR: minimum mandatory ventilation rate.

**Table S2. Pairwise comparisons of Kaplan-Meier curves by Log-rank test (Figure 1).**

Variable	Centers									
	1-2	1-3	1-4	1-5	2-3	2-4	2-5	3-4	3-5	4-5
Freedom from mandatory ventilation	1.000	<0.001	<0.001	<0.001	0.010	<0.001	0.310	<0.001	1.000	<0.001
Freedom from opioid administration	1.000	0.500	<0.001	1.000	1.000	<0.001	1.000	<0.001	1.000	<0.001

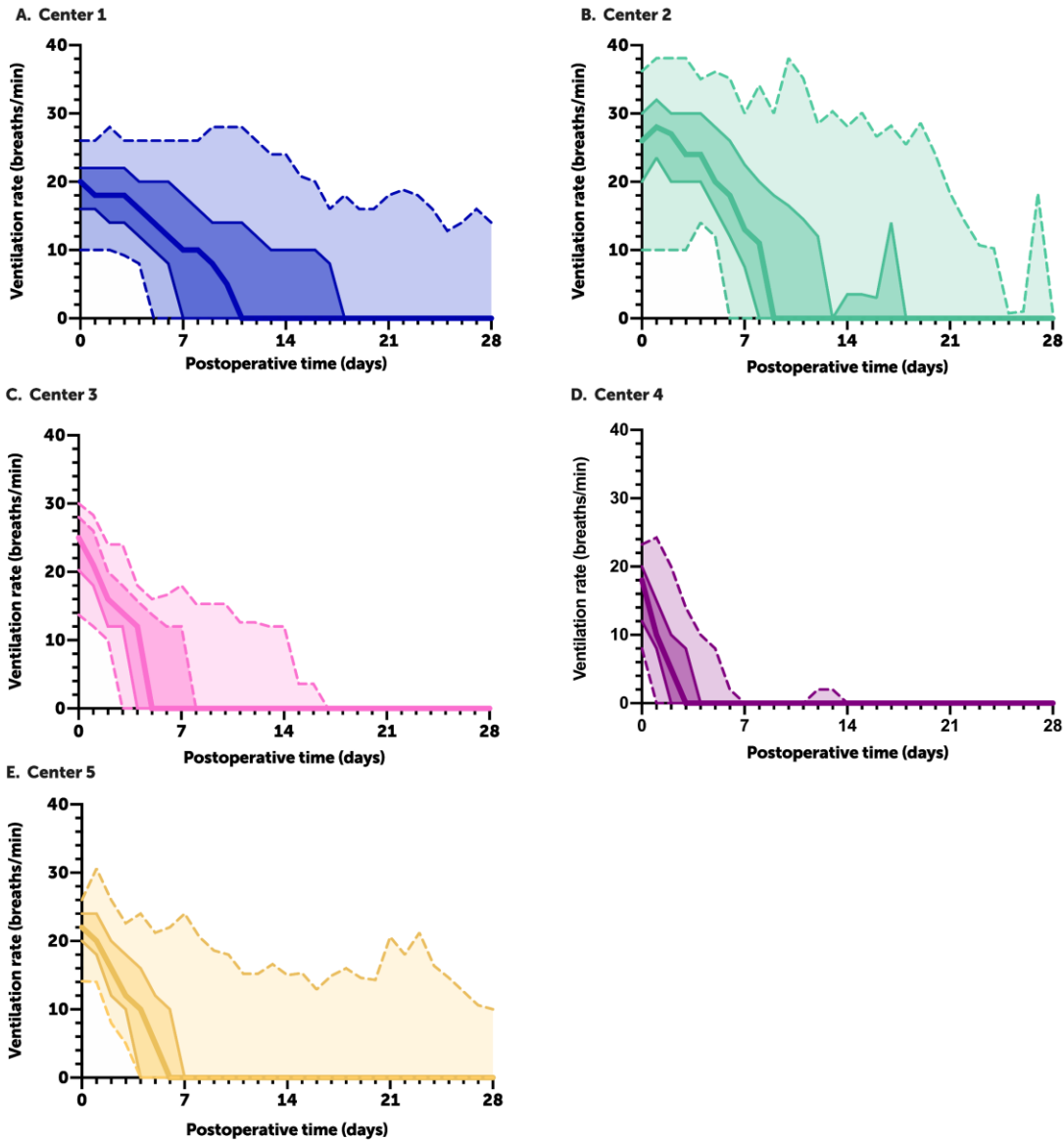
P values are adjusted p values by Bonferroni correction for multiple tests. Significance level is set at two-sided p value <0.05.

**Table S3. Demographic, clinical, surgical details and outcomes of included patients according with era.**

Variable	Total (n=502)	2009-2014 (n=279)	2015-2018 (n=223)	P- value
Age (days), median (IQR)	5 (3-6)	5 (3-6)	5 (3-6)	0.632
Gestational age (weeks), median (IQR)	39 (38-39)	39 (38-39)	39 (38-39)	0.831
Prematurity*, n (%)	38 (8)	20 (7)	28 (8)	0.704
Weight (kg), median (IQR)	3.2 (2.9-3.5)	3.2 (2.8-3.5)	3.2 (3.0-3.5)	<b>0.034</b>
Sex (male), n (%)	330 (66)	180 (65)	150 (67)	0.519
Cardiac diagnosis, n (%)				
HLHS	442 (88)	248 (89)	194 (87)	0.204#
DILV/DIRV	19 (4)	7 (3)	12 (5)	
AV canal, unbalanced	17 (4)	7 (3)	10 (5)	
DORV, hypo LV	8 (2)	6 (2)	2 (1)	
TA	14 (3)	9 (3)	5 (2)	
Other	2 (0)	2 (1)	0 (0)	
Surgical characteristics				
Type of Shunt, n (%)				
Blalock-Taussig shunt	173 (34)	111 (40)	62 (28)	<b>0.005</b>
Sano shunt	329 (66)	168 (60)	161 (72)	
CPB time (min)	166 (140-206)	161 (141-296)	183 (138-222)	<b>0.004</b>
DHCA time (min)	10 (4-26)	10 (6-28)	9 (4-21)	<b>0.022</b>
Aortic clamp time (min)	78 (60-105)	82 (64-110)	73 (58-97)	<b>0.005</b>
ECMO support				
ECMO support within 28 days, n (%)	50 (10)	27 (10)	23 (10)	0.813
Failure to wean from CPB, n (%)	23 (5)	10 (4)	13 (6)	0.232
Time from surgery to ECMO (days), median (IQR)	1 (0-9)	1 (0-15)	0 (0-3)	0.134
ECMO duration (days), median (IQR)	5 (3-10)	4 (2-11)	6 (3-8)	0.463
Mandatory ventilation				
Length of mandatory ventilation (days), median (IQR)	8 (5-16)	8 (5-15)	9 (5-17)	0.238
Minimum ventilation rate per day (breaths/min), median (IQR)**	14 (11-17)	14 (10-16)	14 (12-18)	0.002
Opioid use				
First line opioid infusion, n (%)				
Fentanyl	334 (66)	184 (66)	150 (67)	0.756
Morphine	168 (34)	95 (34)	73 (32)	
Length of opioid administration (days), n (%)	13 (8-25)	13 (8-24)	14 (9-26)	<b>0.035</b>
Opioid TDD (morphine equivalents, mg/kg/day), median (IQR)**	0.57 (0.16-1.65)	0.50 (0.19-1.42)	0.64 (0.15-2.08)	0.413
Fluid management				
Daily intake (ml/kg/day), median (IQR)**	136 (124-152)	136 (121-152)	137 (125-150)	0.565
Daily output (ml/kg/day), median (IQR)**	108 (94-122)	106 (93-120)	111 (95-125)	<b>0.044</b>
Daily fluid balance (ml/kg/day), median (IQR)**	25 (15-39)	27 (15-40)	24 (14-39)	0.163
Patients' outcomes				
CICU length of stay (days), median (IQR)	16 (10-28)	17 (11-26)	16 (10-31)	0.634
Hospital length of stay (days), median (IQR)	34 (23-56)	34 (23-53)	35 (24-62)	0.421
Survival at 30 days, n (%)	473 (94)	264 (95)	209 (94)	0.667
Survival at discharge, n (%)	444 (88)	246 (88)	198 (89)	0.830

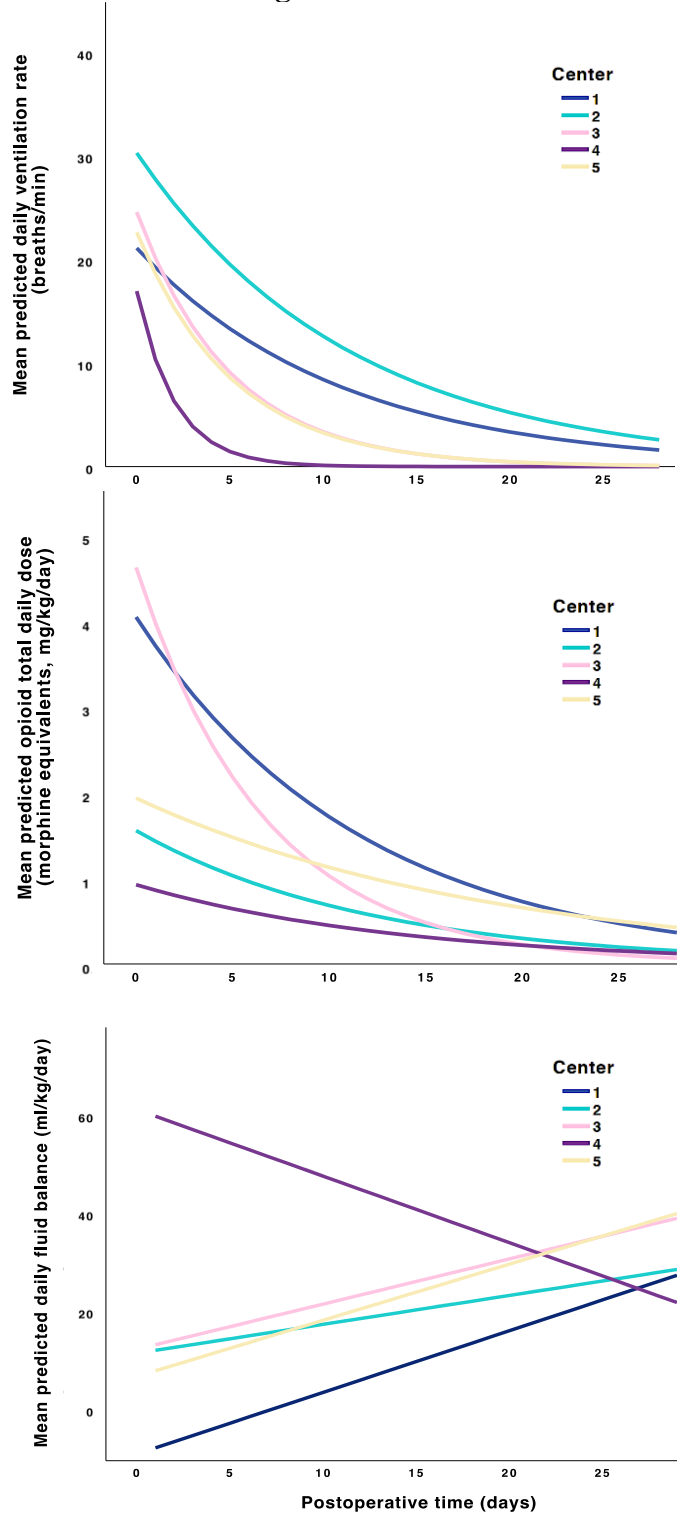
\*Prematurity is defined as <37 weeks estimated gestational age; \*\*values are medians (IQR) of median ventilation rate per day per patient; \*\*\*, ICU and hospital LOS identical at Center 2 due to a center-specific care model dictating location of care; #Fisher's Exact test. AV: atrioventricular; CICU: cardiac intensive care unit; CPB: cardiopulmonary bypass; DHCA: deep hypothermic cardiac arrest; DILV: double inlet left ventricle; DIRV: double inlet right ventricle; DORV: double outlet right ventricle; ECMO: extracorporeal membrane oxygenation; HLHS: hypoplastic left heart syndrome; IQR: inter-quartile range; LV: left ventricle; POD: post-operative day; TA: tricuspid atresia; TDD: total daily dose. Missing data, n: age, 13; gestational age, 92; CBP, DHCA, aortic clamp times: 1; CICU and hospital length of stay, 4.

**Figure S1. Care curves for minimum mandatory mechanical ventilation rate for POD 0-28 at Centers 1 through 5 demonstrate important differences among groups.**



For example, at Center 5, 50% of patients were weaned to a ventilator rate of 10 (and thus doing the majority of their own work of breathing) by POD 4, a milestone that was not reached until POD 7-8 at Centers 1 and 2. The median time between reaching a rate of 10 and a rate of 0 (pressure support ventilation) also differed among centers, and was as high as 4 days at Center 1 and low as 1 day at Center 2. Dark center line = median; dark shaded and solid middle lines = interquartile range; light shaded and dotted outer lines = 5 and 95%.

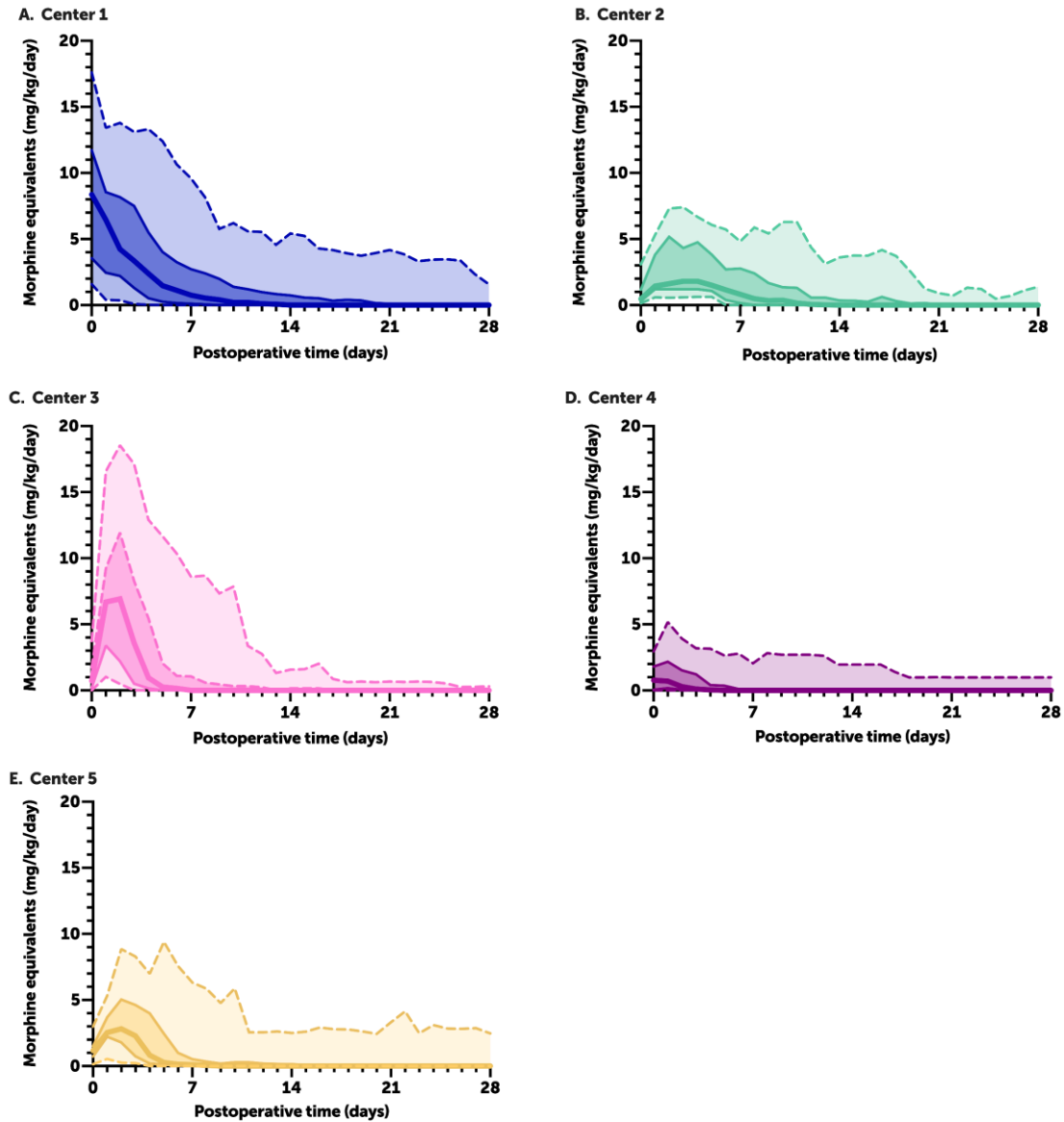
**Figure S2. Estimated mean values of daily ventilation rate, opioid total daily dose, and daily fluid balance over time according to center affiliation.**





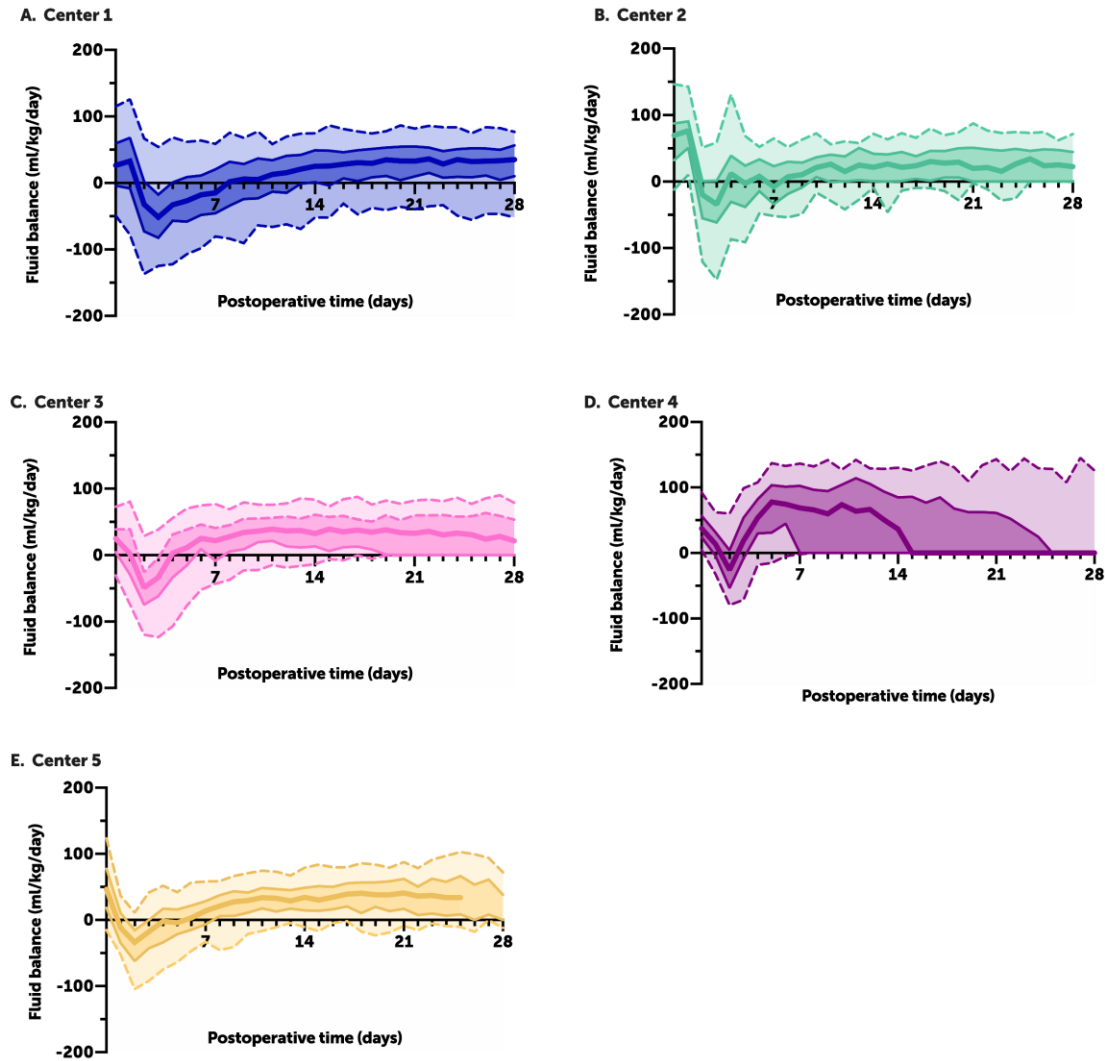
When adjusted for baseline characteristics, center affiliation is still an independent predictor of ventilation rate, opioid total daily dose and fluid balance trajectories over time and daily changes. Fitted distributions are logarithmic for ventilation rate and opioid total daily dose, linear for daily fluid balance. Models are adjusted for age, diagnosis (HLHS/not HLHS), shunt type, surgical times (CBP time, DHCA time, aortic clamp time), ECMO support in the 28 PODs (yes/no). Reference categories for adjusting binary factors are HLHS, Sano, no ECMO. N observations included for modeling: mandatory ventilation N=14152 (97%), opioid administration N=14117 (97%), fluid balance N=14152 (97%).

Figure S3. Care curves opioid total daily dose for POD 0-28 at Centers 1 through 5.



The median narcotic dose on POD 2 at Center 2 was 1.6 mg/kg/day morphine equivalents and at Center 3 was 6.9 mg/kg/day. The rate of opioid weaning following the peak (most often on POD 2) also varied from a daily wean of 1.4 mg/kg/day (Center 3) to 0.5 mg/kg/day (Center 5). Dark center line = median; dark shaded and solid middle lines = interquartile range; light shaded and dotted outer lines = 5 and 95%.

Figure S4. Care curves daily fluid balance for POD 0-28 at Centers 1 through 5.



Center 1 had a median fluid balance of -51 mL/kg/day on POD 3, a time when median fluid balance ranged between -34 to +18 mL/kg/day at the remaining 4 centers. Dark center line = median; dark shaded and solid middle lines = interquartile range; light shaded and dotted outer lines = 5 and 95%.