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ORIGINAL ARTICLE

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Predictors of extracorporeal membrane oxygenation support after surgery for adult congenital heart disease in children's hospitals

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Abstract

Objective: Adult congenital heart disease (ACHD) patients who undergo cardiac surgery are at risk for poor outcomes, including extracorporeal membrane oxygenation support (ECMO) and death. Prior studies have demonstrated risk factors for mortality, but have not fully examined risk factors for ECMO or death without ECMO (DWE). We sought to identify risk factors for ECMO and DWE in adults undergoing congenital heart surgery in tertiary care children's hospitals.

Design: All adults (≥18 years) undergoing congenital heart surgery in the Pediatric Health Information System (PHIS) database between 2003 and 2014 were included. Patients were classified into three groups: ECMO-free survival, requiring ECMO, and DWE. Univariate analyses were performed, and multinomial logistic regression models were constructed examining ECMO and DWE as independent outcomes.

Setting: Tertiary care children's hospitals.

Results: A total of 4665 adult patients underwent ACHD surgery in 39 children's hospitals with 51 (1.1%) patients requiring ECMO and 64 (1.4%) patients experiencing DWE. Of the 51 ECMO patients, 34 (67%) died. Increasing patient age, surgical complexity, diagnosis of single ventricle heart disease, preoperative hospitalization, and the presence of noncardiac complex chronic conditions (CCC) were risk factors for both outcomes. Additionally, low and medium hospital ACHD surgical volume was associated with an increased risk of DWE in comparison with ECMO.

Conclusions: There are overlapping but separate risk factors for ECMO support and DWE among adults undergoing congenital heart surgery in pediatric hospitals.

KEYWORDS
adult congenital heart disease, congenital heart surgery, extracorporeal membrane oxygenation

Abbreviations: ACHD, adult congenital heart disease; CCC, complex chronic conditions; CHD, congenital heart disease; DWE, death without extracorporeal membrane oxygenation support; ECMO, extracorporeal membrane oxygenation; EFS, extracorporeal membrane oxygenation-free survival; PHIS, pediatric health information systems; RACHS-1, risk adjustment for congenital heart surgery-1; RR, relative risk.

1 | INTRODUCTION

The number of adult congenital heart disease (ACHD) patients is rising and now exceeds the number children with congenital heart disease (CHD).[1,2] Many CHD patients will require cardiac surgery in adulthood, and ACHD surgery has an in-hospital mortality rate of 1.8%-2.2%.[3-5] While the risk of poor surgical outcomes is well defined for congenital heart surgery in children, much less is known about predictors of poor outcomes in ACHD surgery. Previous studies of ACHD surgery reported age, male sex, surgical complexity, payer, and hospital surgical volume as risk factors.[3,6]

Pediatric cardiac surgical programs routinely use extracorporeal membrane oxygenation (ECMO) to rescue surgical patients with cardiopulmonary failure, and predictors of ECMO support in these patients have been well documented.[7-11] However, predictors of ECMO support in adults after CHD surgery have not been previously reported. Because adult patients are likely to be active participants in their medical decision making, identifying patients who are at increased risk of requiring ECMO support is important for presurgical discussion and planning. While ECMO is a lifesaving therapy, it is highly invasive, resource intensive, and costly, with many attendant risks, including stroke, bleeding, and limb ischemia.[12,13] As such, some patients, providers, and families may choose to forgo ECMO support and risk the possibility of experiencing death without ECMO (DWE) after ACHD surgery; additionally some patients may be excluded from ECMO due to other risk factors.

Currently, only a few reports have described factors associated with DWE in specific groups of children.[8,14] Thus, understanding risk factors for ECMO support and DWE in ACHD surgical patients will improve presurgical discussion and planning in this population. For these reasons, we utilized a large administrative dataset to identify risk factors for ECMO and DWE in adults undergoing ACHD surgery in children's hospitals.

2 | METHODS

We performed a retrospective, cross-sectional study using the Pediatric Health Information System (PHIS) database, which includes administrative and billing data from 48 tertiary care children's hospitals in the United States. The PHIS database includes patient demographics, diagnoses, procedures, billing data, and outcomes. This study utilized data without any patient identifying information and was exempted from human subjects review by the Institutional Review Board of the University of Utah (PI: SLB).

All patients aged 18-49 who were discharged from a PHIS hospital between January 1, 2004 and June 30, 2014 and had undergone congenital heart surgery were included. We excluded adults above the age of 49 to limit the role of acquired heart disease, similar to multiple other publications evaluating adults with congenital heart disease using this dataset.[3,15,16] We excluded hospitals (n = 8) that did not have data available for adult congenital heart surgery hospitalizations as well as those that did not perform ECMO on any patients after cardiac surgery (n = 1) during the time period. Using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure and diagnostic codes, patients were assigned a Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) Category[17] to categorize surgical complexity. As the only surgical stratification method that has been routinely applied to ICD-9-CM diagnosis and procedure codes, RACHS-1 categories range from 1 to 6 with increasing values corresponding to increasing surgical complexity. Patients without a RACHS-1 Category but with procedure codes consistent with a cardiac surgical procedure (cardiopulmonary bypass, hypothermia related to cardiac surgery, cardioplegia, intraoperative pacemaker, or shunts that may be performed off bypass) were included and classified as "unassigned." Patients undergoing heart transplants were included in our analysis. Similar to previous work,[3] we grouped patients with a RACHS-1 Category of 5-6 with Category 4 due to their low frequency in the adult population. Additionally, RACHS-1 Category 1 and 2 patients were combined into a single baseline group due to the similar outcomes in these two groups.[3]

Specific cardiac surgery procedures were identified using appropriate ICD-9-CM procedure codes and complications were identified using ICD-9-CM diagnostic codes. Patients were categorized into the following age groups: 18-19 years, 20-24 years, 25-34 years, and 35-49 years. Primary payer was classified as government (including Medicaid, Medicare, or other government insurance) and other payer (including private). Cardiovascular risk factors were also identified using ICD-9-CM diagnostic codes. Centers which performed fewer than 10 ACHD surgical cases per year were defined as low volume, those that performed 10-19 cases per year were classified as medium volume, and those that performed 20 or more cases per year were classified as high-volume.[3] Patients with an ICD-9-CM code of 746.7 (hypoplastic left heart syndrome), 746.1 (tricuspid atresia), or 745.3 (common ventricle) were categorized as having single ventricle heart disease.

As a marker of severity of illness, preoperative hospitalization was defined by surgery performed after the day of admission. Patients with a preoperative hospitalization were further classified into three categories: (1) patients hospitalized for presumed anticoagulation management (patients with an ICD-9-CM code of V58.61 [long-term (current) use of anticoagulants] without preoperative vasopressor use), (2) those with preoperative vasopressor use (PHIS Pharmacy codes for milrinone, epinephrine, dobutamine, dopamine, norepinephrine, phenylephrine, isoproterenol, or vasopressin before the day of surgery), and (3) other (those not classified in the previous two categories). Patient complexity was also assessed by the presence of noncardiac complex chronic conditions (CCC) as described by Feudtner and colleagues.[18] The number of involved CCC organ systems was categorized as 0, 1, or 2+.

The dependent outcome was determined by ECMO utilization and hospital survival status. Patients were classified as having ECMO-free survival (EFS: survival to hospital discharge without requiring ECMO support), requiring ECMO support (including both patients that survived to hospital discharge and those that died on or after receiving ECMO support), or DWE. Because patients that die without ECMO support are unlikely to resemble patients that have ECMO-free survival and are also different from patients that receive ECMO, we analyzed these outcomes as distinct endpoints. Conceptually, outside of obvious contraindications, patients that die without ECMO may possibly have survived to discharge if they had received ECMO support. We performed univariate analyses of possible risk factors for ECMO and DWE. Additionally, we performed a univariate analysis for survival among patients who received ECMO. We also evaluated possible factors that may influence decision making in regards to ECMO utilization vs death without ECMO. For example, clinically important bleeding is often a contraindication for ECMO and may be more common among patients who die without ECMO. Finally, we performed an exploratory univariate analysis of patients with a single ventricle diagnosis evaluating risk factors for ECMO and DWE. The chi-square and Fisher's exact tests were used to examine categorical data as appropriate.

We constructed multivariable multinomial regression models examining the three possible outcomes: EFS, ECMO, and DWE. Given the small number of patients experiencing ECMO or DWE, the relatively short duration of postoperative hospitalizations, and the lack of granularity in regards to time measurement in PHIS, multinomial regression models were used to analyze these outcomes. We included variables from the univariate analysis with a *P* value <.20 and required a *P* value of <.05 for persistence in the model. Two multinomial models were created. We created our primary model by starting with variables previously associated with mortality as reported by Kim et al[3] and subsequently adding other variables to this model that could be known preoperatively, as described above. The primary multinomial model included all variables noted to be independently associated with at least one of the outcomes of ECMO or DWE in comparison with EFS with a *P* value <.05. We also computed the risks for DWE in comparison with ECMO. To further evaluate the role of specific CCC in our model, we also created an exploratory model that included indicator variables for each organ system CCC in the place of the ordinal CCC variable in the primary model (as described above). Stata/SE (version 14.2; StataCorp LLC, College Station, Texas) was used for data analysis.

TABLE 1 Adult congenital heart disease surgery discharge characteristics (n = 4665)

	n (%)
Age, years	
18-19	1394 (30)
20-24	1463 (31)
25-34	1194 (26)
35-49	614 (13)
Male	2513 (54)
Race	
Non-Hispanic white	3413 (73)
Non-Hispanic black	360 (8)
Hispanic	295 (6)
Asian	133 (3)
Other	334 (7)
Missing	130 (3)
Payer	
Government	1352 (29)
Other	3313 (71)
RACHS-1 Category	
1-2	1978 (42)
3	1892 (41)
4+	179 (4)
Unclassified	616 (13)
Single ventricle	302 (6)
Preoperative hospitalization	815 (17)
Adult annual surgical volume	
Low (fewer than 10 cases per year)	1531 (33)
Medium (10-19 cases per year)	1552 (33)
High (20 or more cases per year)	1582 (34)
Number of noncardiac CCC	
0	3493 (75)
1	940 (20)
2+	232 (5)

Abbreviations: CCC, complex chronic conditions; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1.

3 | RESULTS

We identified 4665 adult patients who underwent ACHD surgery at 39 PHIS hospitals in the study period. The median age at admission was 22 years (IQR: 19-29 years). Demographic characteristics are found in Table 1. The majority of patients (n = 2857, 61%) were 18-24 years old, 2513 (54%) of patients were male and 42% underwent either a RACHS-1 Category 1 or 2 procedure. Of the 302 patients with a single ventricle diagnosis, 169 (56%) had tricuspid atresia, 95 (31%) had a common ventricle, and 38 (13%) had hypoplastic left heart syndrome. Only 815 (17%) patients were hospitalized preoperatively with a median preoperative hospitalization duration of 2 days (IQR 1-6 days). A minority of patients (n = 1172, 25%) had at least one CCC. The most common CCC were "other congenital or genetic defect" (n = 576, 12%), metabolic (n = 229, 5%), renal and urologic (n = 166, 4%), neurologic and neuromuscular (n = 161, 3%), and hematologic or immunologic (n = 146, 3%). Surgeries were performed at 5 high-volume hospitals, 10 medium volume hospitals, and 24 low volume hospitals; similar numbers of surgeries were performed in each volume group.

Demographic and clinical information by outcome group (EFS, ECMO, and DWE) is shown in Table 2. While the majority (n = 4550, 97.5%) of patients had EFS, a small proportion of patients required ECMO (n = 51, 1.1%) or had DWE (n = 64, 1.4%). Of the 51 ECMO patients, 34 (67%) died. The overall surgical mortality rate was 2.1%

TABLE 2 Characteristics of adult congenital heart disease surgical patients by outcome

	EFS *n* = 4550	ECMO *n* = 51	DWE *n* = 64	*P* value
Age, years				.01
18-19	1368 (30)	12 (24)	14 (22)	
20-24	1436 (32)	12 (24)	15 (23)	
25-34	1160 (26)	16 (31)	18 (28)	
35-49	586 (13)	11 (22)	17 (27)	
Male	2439 (54)	31 (61)	43 (67)	.06
Race				.28
Non-Hispanic white	3333 (73)	37 (73)	43 (67)	
Non-Hispanic black	351 (8)	5 (10)	4 (6)	
Hispanic	287 (6)	1 (2)	7 (11)	
Asian	131 (3)	0 (0)	2 (3)	
Other	323 (7)	7 (14)	4 (6)	
Missing	125 (3)	1 (2)	4 (6)	
Government payer	1302 (29)	23 (45)	27 (42)	<.01
Cardiovascular risk factors				
Hypertension	621 (14)	8 (16)	9 (14)	.91
Hyperlipidemia	58 (1)	1 (2)	3 (5)	.06
Coronary artery disease	146 (3)	8 (16)	1 (2)	<.01
Atrial fibrillation/flutter	501 (11)	19 (37)	22 (34)	<.01
Type 1 diabetes mellitus	25 (1)	0 (0)	1 (2)	.48
Type 2 diabetes mellitus	40 (1)	1 (2)	5 (8)	<.01
Chronic kidney disease	46 (1)	2 (4)	7 (11)	<.01
RACHS-1 Category				<.01
1-2	1963 (43)	6 (12)	9 (14)	
3	1846 (41)	19 (37)	27 (42)	
4+	163 (4)	11 (22)	5 (8)	
Unclassified	578 (13)	15 (29)	23 (36)	
Single ventricle	270 (6)	14 (27)	18 (28)	<.01
Specific procedures				
Pulmonary valve repair/replacement	1616 (36)	8 (16)	6 (9)	<.01
Aortic valve repair/replacement	919 (20)	11 (22)	8 (13)	.30
Atrioventricular valve repair/replacement	855 (19)	8 (16)	15 (23)	.54
Atrial septal defect closure	748 (16)	6 (12)	3 (5)	.03
Fontan or Fontan revision	206 (5)	9 (18)	10 (16)	<.01
Heart transplant	119 (3)	10 (20)	11 (17)	<.01
Preoperative hospitalization				<.01
No preoperative hospitalization	3800 (84)	17 (33)	33 (52)	
Preoperative hospitalization for anticoagulation	43 (1)	3 (6)	2 (3)	
Preoperative hospitalization with vasopressors	381 (8)	9 (18)	21 (33)	
Preoperative hospitalization without anticoagulation or vasopressors	326 (7)	22 (43)	8 (13)	
Adult annual surgical volume				.05
Low (fewer than 10 cases per year)	1493 (33)	14 (28)	24 (38)	
Medium (10-19 cases per year)	1514 (33)	12 (24)	26 (41)	
High (20 or more cases per year)	1543 (34)	25 (49)	14 (22)	

(Continues)

TABLE 2 (Continued)

	EFS *n* = 4550	ECMO *n* = 51	DWE *n* = 64	*P* value
Number of noncardiac CCC				<.01
0	3475 (76)	10 (20)	8 (13)	
1	880 (19)	30 (59)	30 (47)	
2+	195 (4)	11 (22)	26 (41)	
Specific CCC				
Gastrointestinal	85 (2)	2 (4)	7 (11)	<.01
Hematologic or immunologic	136 (3)	3 (6)	7 (11)	<.01
Metabolic	210 (5)	6 (12)	13 (20)	<.01
Neurologic and neuromuscular	122 (3)	12 (24)	27 (42)	<.01
Renal and urologic	123 (3)	19 (37)	24 (38)	<.01
Respiratory	50 (1)	7 (14)	9 (14)	<.01
Malignancy	27 (1)	0 (0)	1 (2)	.50
Other congenital or genetic condition	560 (12)	8 (16)	8 (13)	.77

Abbreviations: CCC, complex chronic conditions; DWE, death without extracorporeal membrane oxygenation; ECMO, extracorporeal membrane oxygenation; EFS, ECMO-free survival ; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1.

(*n* = 98). Patients who received ECMO support or had DWE were older, were more likely to have governmental insurance, were more likely to have cardiovascular risk factors, underwent higher complexity procedures, were more likely to have single ventricle anatomy, were more likely to have been hospitalized preoperatively, and had a higher number of CCC. Typically straightforward surgical procedures (such as pulmonary valve replacement and atrial septal defect closure) demonstrated lower rates of ECMO and DWE, while the Fontan operation and heart transplant were associated with higher rates of ECMO and DWE. Additionally, univariate analysis demonstrated an association between adult annual surgical volume and the outcomes, with low and medium volume hospitals under-represented in the ECMO group and over-represented comparatively in the DWE group.

Among patients that died without ECMO, 9 patients underwent cardiac transplantation as their initial operation during hospitalization while two patients underwent transplantation after a previous cardiac procedure. Among patients that received ECMO, 5 patients underwent cardiac transplantation as the initial operation with subsequent ECMO support. Five other patients underwent a previous cardiac procedure followed by subsequent cardiac transplantation. In this group of patients, three of the five patients received ECMO support after the initial operation and before cardiac transplantation while two patients received ECMO support after cardiac transplantation.

In order to further evaluate predictors of survival in patients who were placed on ECMO, we also compared ECMO survivors and non-survivors (Table 3). No significant differences between outcomes were noted among any of the analyzed variables, likely related to the small sample size of patients who were placed on ECMO.

Additionally, in order to evaluate possible differences between patients who experienced DWE instead of ECMO support, we analyzed factors that may influence decision making regarding ECMO (Table 4). Gastrointestinal bleeding, seizures, and stroke were more common in DWE patients than ECMO patients while postoperative bleeding was more common in ECMO patients.

In an effort to better understand outcomes of single ventricle patients, we performed an exploratory analysis of patient characteristics and outcomes limited to only single ventricle patients (Supplementary Table). Many characteristics were similar between the three outcomes, but preoperative hospitalization and number of CCC were increased among patients who experienced ECMO or DWE. Coronary artery disease and chronic kidney disease were increased among patients with ECMO and DWE, respectively. Additionally, all of the evaluated factors that may affect ECMO decision making with the exception of intracranial hemorrhage were increased among ECMO and DWE patients.

We then created a multivariate multinomial model using demographic and preoperative variables for the outcomes of ECMO and DWE with ECMO-free survival as the base outcome (Figure 1). In this model, older age group, male gender, increasing surgical complexity, lower annual adult surgical volume, single ventricle diagnosis, preoperative hospitalization, and the presence of 1 or more CCC were associated with at least one of the outcomes of ECMO or DWE. While several of the risk factors overlapped for both outcomes, there were also some differences noted, with differential associations noted among gender, RACHS-1 categories, annual adult surgical volume, and preoperative hospitalization, as described below.

Several factors were associated with increased risk of ECMO when compared to ECMO-free survival. Age 35-49 years [relative risk (RR): 2.0, 95% confidence interval (CI): 1.001-3.9], coronary artery disease (RR 4.4, 95% CI: 1.8-11.3), RACHS-1 Category 3 (RR: 2.6, 95% CI: 1.01-6.6), Category 4+ (RR: 10.6, 95% CI: 3.1-36.3) or unclassified (RR: 3.6, 95% CI: 1.01-13.0) procedure, single ventricle diagnosis (RR: 2.9, 95% CI: 1.4-5.8), and other preoperative

TABLE 3 Characteristics of patients supported with ECMO after adult congenital heart disease surgery by survival status

	ECMO survivors *n* = 17	ECMO nonsurvivors *n* = 34	*P* value
Age, years			.57
18-19	6 (35)	6 (18)	
20-24	4 (24)	8 (24)	
25-34	4 (24)	12 (35)	
35-49	3 (18)	8 (24)	
Male	11 (65)	20 (59)	.69
Race			.86
Non-Hispanic white	13 (76)	24 (71)	
Non-Hispanic black	1 (6)	4 (12)	
Hispanic	0 (0)	1 (3)	
Asian	0 (0)	0 (0)	
Other	3 (18)	4 (12)	
Missing	0 (0)	1 (3)	
Government payer	7 (41)	16 (47)	.69
RACHS-1 Category			.61
1-2	2 (12)	4 (12)	
3	5 (29)	14 (41)	
4+	3 (18)	8 (24)	
Unclassified	7 (41)	8 (24)	
Single ventricle	2 (12)	12 (35)	.10
Preoperative hospitalization			.14
No preoperative hospitalization	8 (47)	9 (26)	
Preoperative hospitalization for anticoagulation	2 (12)	1 (3)	
Preoperative hospitalization with vasopressors	3 (18)	6 (18)	
Preoperative hospitalization without anticoagulation or vasopressors	4 (24)	18 (53)	
Adult annual surgical volume			.38
Low (fewer than 10 cases per year)	6 (35)	8 (24)	
Medium (10-19 cases per year)	2 (12)	10 (29)	
High (20 or more cases per year)	9 (53)	16 (47)	
Number of noncardiac CCC			.85
0	4 (24)	6 (18)	
1	10 (59)	20 (59)	
2+	3 (18)	8 (24)	
Specific CCC			
Gastrointestinal	0 (0)	2 (6)	.55
Hematologic or immunologic	1 (6)	2 (6)	1.00
Metabolic	1 (6)	5 (15)	.65
Neurologic and neuromuscular	4 (24)	8 (24)	1.00
Renal and urologic	6 (35)	13 (38)	.83
Respiratory	3 (18)	4 (12)	.67
Other congenital or genetic condition	1 (6)	7 (21)	.24

Abbreviations: CCC, complex chronic condition; ECMO, extracorporeal membrane oxygenation; RACHS-1, Risk Adjustment for Congenital Heart Surgery-1.

TABLE 4 Comparison of factors between patients receiving ECMO and DWE

	ECMO (n = 51)	DWE (n = 64)	P value
Gastrointestinal bleeding	1 (2)	9 (14)	.02
Seizures	5 (10)	18 (28)	.02
Thromboembolic stroke	6 (12)	20 (31)	.01
Intracranial hemorrhage	1 (2)	1 (2)	1.00
Acute renal failure	35 (69)	35 (55)	.13
Liver failure	9 (18)	4 (6)	.06
Sepsis	11 (22)	17 (27)	.54
Postoperative renal support	26 (51)	24 (38)	.15
Postoperative bleeding	31 (61)	20 (31)	<.01

Abbreviations: DWE, death without extracorporeal membrane oxygenation; ECMO, extracorporeal membrane oxygenation.

hospitalization (RR: 11.3, 95% CI: 5.7-22.5) were associated with requiring ECMO support. Patients at medium volume hospitals were at decreased risk of ECMO (RR: 0.3, 95% CI: 0.2-0.7) in comparison to high-volume hospitals, while those at low volume hospitals did not have a significant difference noted. An increasing number of CCC was associated with an increasing risk of ECMO (one CCC RR: 10.6, 95% CI: 4.5-24.7; 2 + CCC RR: 14.2, 95% CI 6.3-31.8).

Similarly, several factors were associated with DWE in comparison to ECMO-free survival. Age 35-49 years (RR: 3.7, 95% CI: 1.5-9.2), male gender (RR: 1.8, 95% CI: 1.05-3.2), type 2 diabetes mellitus (RR: 2.9, 95% CI: 1.2-7.2), RACHS-1 Category 3 (RR: 2.5, 95% CI: 1.1-5.7) and unclassified (RR: 3.9, 95% CI: 1.6-9.5) procedures, low hospital surgical volume (RR: 2.3, 95% CI: 1.05-5.3), single ventricle diagnosis (RR 3.1, 95% CI 1.4-6.8), and preoperative hospitalization with vasopressor use (RR 2.3, 95% CI 1.2-4.4) were associated with DWE. An increasing number of CCC was associated with increased risk of DWE (one CCC RR: 13.6, 95% CI: 6.5-28.4; 2 + CCC RR: 39.1, 95% CI 15.9-96.1).

In the same model, we examined risk factors for DWE in comparison to ECMO (Figure 2). Admission to low (RR: 4.0, 95% CI: 1.5-10.9) and medium (RR: 4.6, 95% CI: 1.7-12.3) volume hospitals was associated with DWE vs ECMO. Additionally, coronary artery disease (RR 0.05, 95% CI: 0.005-0.6) and other preoperative hospitalization (RR 0.2, 95% CI: 0.1-0.4) were associated with decreased risk of DWE when compared with ECMO.

Finally, we evaluated organ system–specific CCC by including them in the primary model in place of the number of CCC (effect of specific CCC shown in Figure 3). Gastrointestinal CCC was not associated with either outcome, so was removed from the model. The presence of Respiratory, Renal and urologic, and Neurologic and neuromuscular CCC were associated with both ECMO and DWE. Additionally, patients with metabolic and hematologic or immunologic CCC were at increased risk of DWE but not of ECMO.

4 | DISCUSSION

In this large, multicenter study evaluating the outcomes of ECMO and DWE after ACHD surgery, we identified older age, male gender, coronary artery disease, type 2 diabetes mellitus, increased surgical complexity, single ventricle diagnosis, preoperative hospitalization, and number of CCC as risk factors for ECMO and/or DWE. Additionally, lower hospital volume was associated with increased risk of DWE in comparison to ECMO. These findings provide identifiable risk factors for both ECMO support and death without ECMO that can aid preoperative planning and counseling for adult patients undergoing congenital heart surgery.

This study provides multicenter data regarding rates of ECMO use in ACHD patients after cardiac surgery in pediatric hospitals. We identified an ECMO rate of 1.1% after ACHD surgery performed at children's hospitals, similar to a previous single-center report.[19] The population in our study is younger, as would be expected among adults receiving care in children's hospitals. We report a higher rate of ECMO after ACHD surgery than the 0.2% noted in the Nationwide Inpatient Sample.[20] However, the Nationwide Inpatient Sample is composed of a very different patient population, including a broader range of hospitals with many institutions with smaller congenital heart surgery programs that may not routinely perform ECMO.

Our ECMO mortality rate was 67%, which is comparable to previous studies of adults undergoing ACHD surgery[19,20] and non-ACHD-related cardiac surgery.[13,21,22] Although the mortality rate is quite high, the clinical situation was severe enough to lead the providers caring for the patient to pursue invasive support, potentially indicating an otherwise unsatisfactory hemodynamic situation given the known attendant risks of ECMO. We did not identify significant risk factors for mortality among patients placed on ECMO, but this analysis was limited by the low number of patients who received ECMO.

4.1 | Risk factors for ECMO or death without ECMO

In this study, we found that older age, male gender, coronary artery disease, type 2 diabetes mellitus, higher complexity surgery, single ventricle anatomy, preoperative hospitalization, and increasing patient complexity were associated with either ECMO or DWE. In previous analyses of ACHD surgery, male gender and older age have been associated with increased mortality.[3,6] Obesity and diabetes mellitus have been noted to increase postoperative morbidity as well as hospital utilization after cardiac surgery in children's hospitals,[23] but specific effects of diabetes mellitus on mortality in this patient population have not been reported. Limited data regarding the role of coronary artery disease in outcomes after ACHD surgery shows that overall

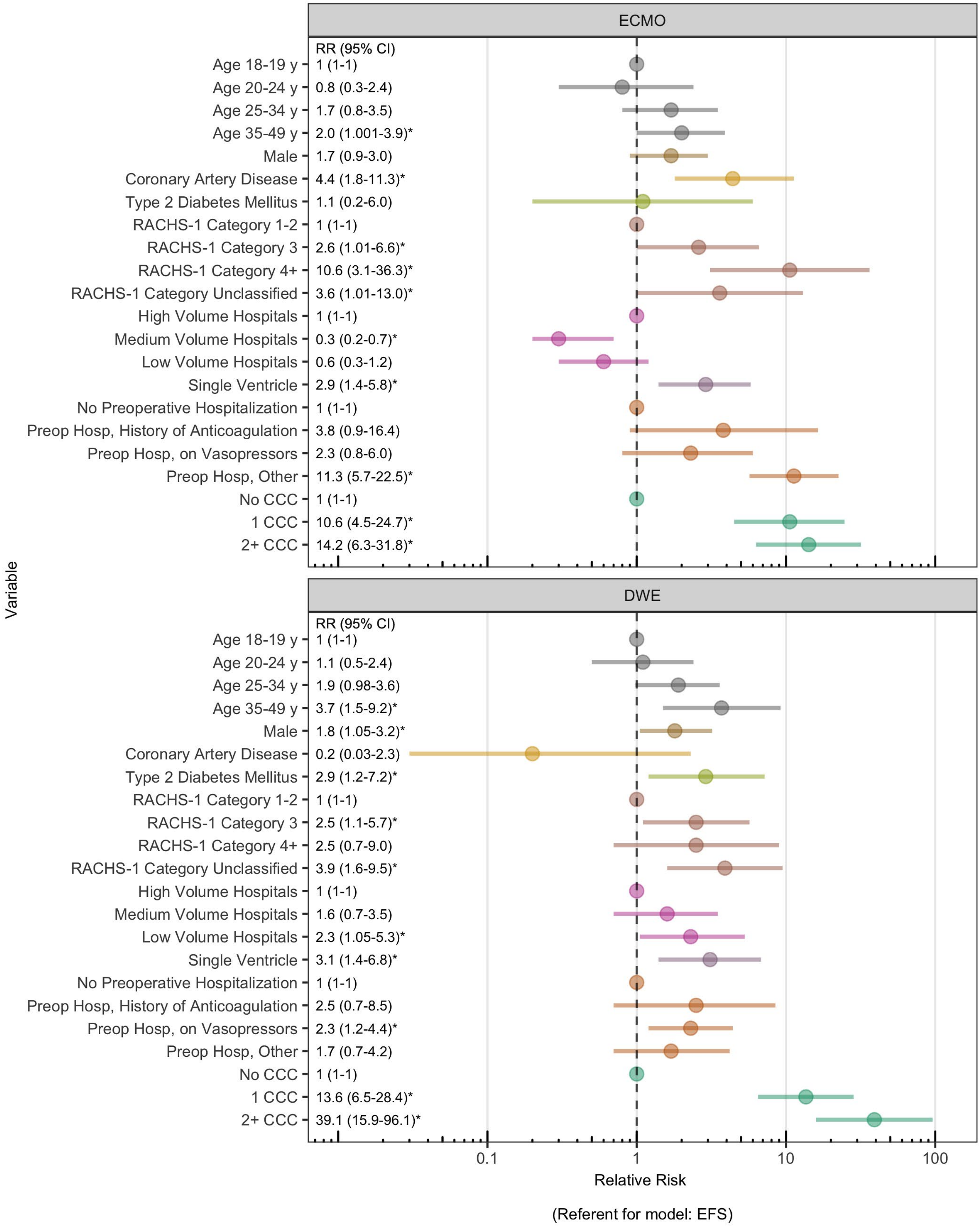

FIGURE 1 Primary multivariate multinomial regression model for ECMO and DWE after ACHD surgery, using EFS as the referent. The reference groups are denoted by the presence of a RR of 1. Abbreviations: ACHD, adult congenital heart disease; CCC, complex chronic conditions; DWE, death without extracorporeal membrane oxygenation; ECMO, extracorporeal membrane oxygenation; EFS, ECMO-free survival; Preop Hosp, preoperative hospitalization; RACHS-1: Risk Adjustment for Congenital Heart Surgery-1. *indicates $P < .05$

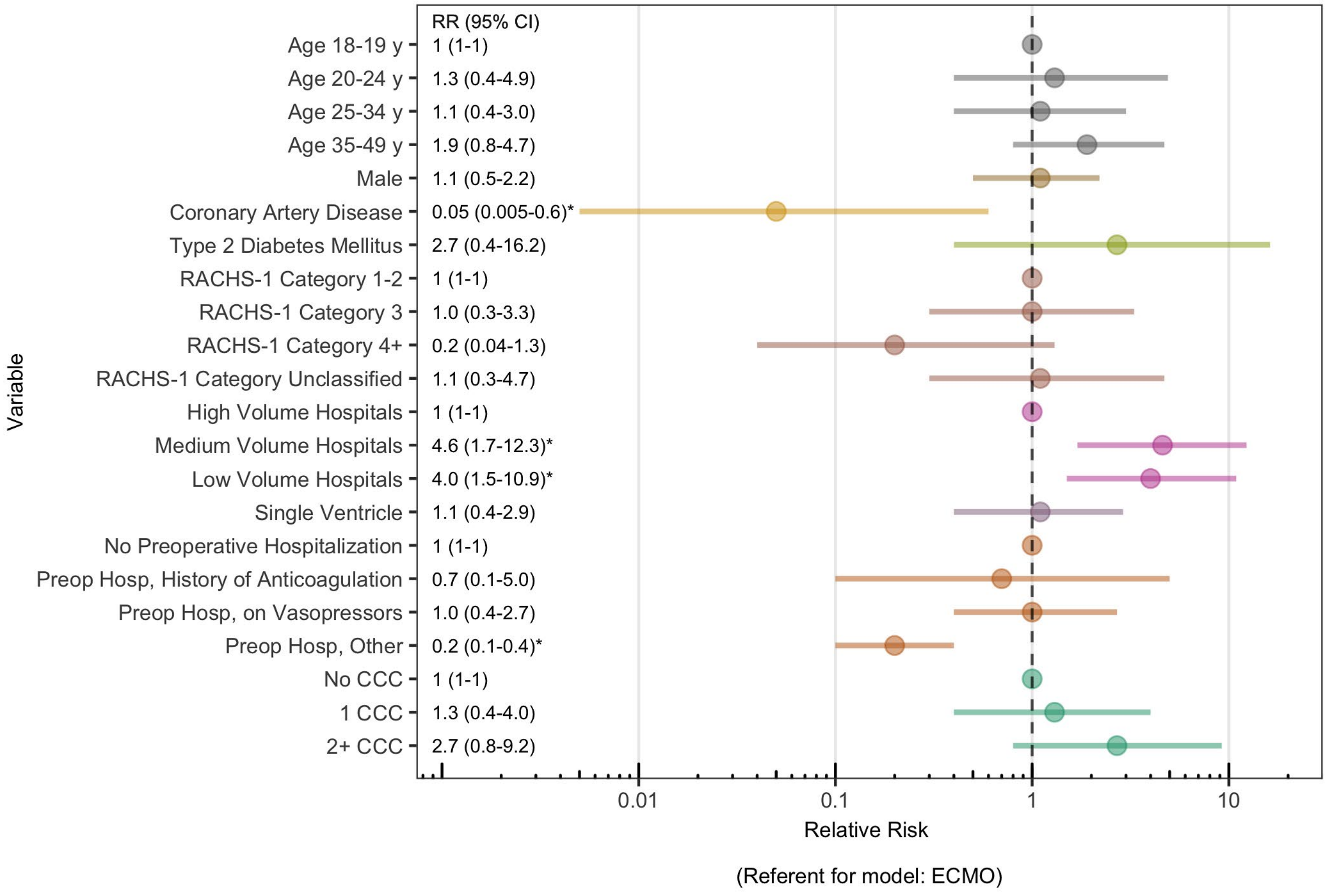

FIGURE 2 Multivariate multinomial regression model for DWE after ACHD surgery in comparison with ECMO. The reference groups are denoted by the presence of a RR of 1. Abbreviations: ACHD, adult congenital heart disease; CCC, complex chronic conditions; DWE, death without extracorporeal membrane oxygenation; ECMO, extracorporeal membrane oxygenation; Preop Hosp, preoperative hospitalization; RACHS-1: Risk Adjustment for Congenital Heart Surgery-1. *indicates $P < .05$

outcomes are similar between matched populations with and without coronary artery bypass grafting, but survival was decreased in certain patient populations, particularly women.[24] We found that coronary artery disease was associated with an increased risk of ECMO but not DWE. Additionally, coronary artery disease was associated with a decreased RR for DWE in comparison with ECMO. This is likely related to the very small number of patients with coronary artery disease in the DWE group as well as the high number of patients with coronary artery disease in the ECMO group (16%). Of note, coronary artery disease was not associated with decreased risk of DWE in comparison with EFS, so it is does not appear to be a protective risk factor. Other literature has also shown that higher complexity surgery is associated with increased risk of ECMO support[10] while single ventricle heart disease is a risk factor for poor outcomes in multiple other studies.[25,26] Finally, an increasing number of CCC has been associated with increased risk of mortality and complications after pediatric cardiac surgery[27] as well as during admission to the pediatric intensive care unit.[28] All of these factors are proxies of underlying patient complexity, supporting the broader theme that medically complex patients are at increased risk of both ECMO support and DWE.

Hospitalization prior to surgical intervention is a risk factor for both ECMO and DWE, but is dependent on the reason for hospitalization. Hospitalized patients with a history of chronic anticoagulation were not at increased risk for either ECMO or DWE. Conversely, patients who were on vasopressors preoperatively (as a proxy for severity of preoperative illness) had an increased risk of DWE but not ECMO. This suggests that greater severity of myocardial dysfunction in the preoperative period influenced the decision not to offer ECMO. This may also suggest that operations in this group were salvage operations used in patients with poor therapeutic alternatives. Finally, patients with a preoperative hospitalization not in one of these categories were at increased risk of ECMO but not DWE. The precise etiology for this is unclear, but the requirement for preoperative hospitalization likely reflects increased disease severity, placing patients at increased risk for need for rescue therapy after surgery. Additionally, it is possible that patients who are admitted preoperatively are more likely to desire all forms of resuscitation including ECMO, making them less likely to die without ECMO support.

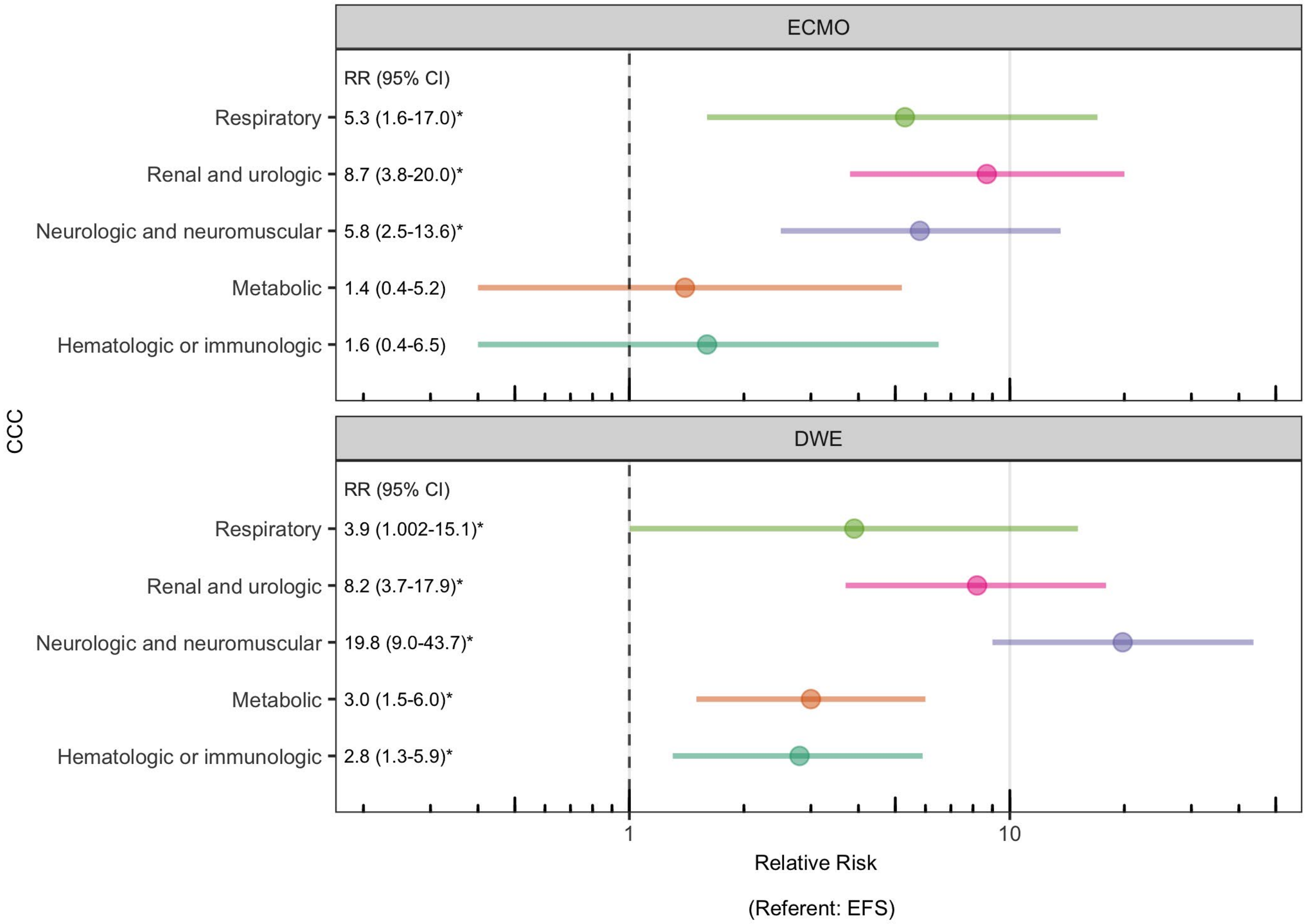

FIGURE 3 Multivariate multinomial regression model for ECMO and DWE after ACHD surgery, including specific CCC categories, using EFS as the referent. The model is adjusted for age group, gender, surgical complexity, cardiac surgical volume, single ventricle diagnosis, and preoperative hospitalization. Abbreviations: ACHD, adult congenital heart disease; CCC, complex chronic conditions; DWE, death without extracorporeal membrane oxygenation; ECMO, extracorporeal membrane oxygenation; EFS, ECMO-free survival. *indicates $P < .05$

Previous studies of adult patients after cardiac surgery have not specifically examined DWE, although this was recently examined after pediatric cardiac surgery.[8,14,29] We found that DWE occurred in 1.4% of adults undergoing ACHD surgery, similar to the rate of 1.6% in pediatric patients with no known genetic condition after cardiac surgery.[8] As stated previously, a proportion of patients that die without ECMO could possibly have survived if they had been supported with ECMO. For this reason, DWE patients could also be considered potential candidates and nonrecipients of ECMO support. Overall, risk factors for DWE are similar to risk factors for ECMO support, and understanding the common risk factors can aid in identifying patients who may require ECMO as well as those who may benefit from additional preoperative planning and discussions. However, patients who die without ECMO are also distinct from patients that require ECMO. Part of the differences between ECMO and DWE patients are contraindications for ECMO, but this potentially does not explain all of the differences.

In our study, DWE patients had higher rates of gastrointestinal bleeding, seizures and thromboembolic stroke than ECMO patients. This suggests that, for about half of all DWE patients (35/64), clinicians and families declined ECMO support due to concerns of further anticoagulation and neurological insult while on ECMO. Because ECMO can contribute to all of the contraindications that we examined and because the timing of diagnoses in PHIS is not recorded, it is unclear if rates of renal/liver failure, sepsis, and postoperative bleeding were comparable in the ECMO and DWE patients at the time ECMO support was being considered. Nonetheless, the care team and the family elected not to place these patients on ECMO when they were experiencing cardiopulmonary failure. Thus, DWE is a consequence of the decision not to place patients with cardiopulmonary failure on ECMO support and instead to allow them possibly to die without further intervention. Practically, this study does not identify patients who are at risk for dying without ECMO; instead, we are identifying risk factors for patients who may potentially be candidates for ECMO but who instead die without further intervention. Identification of these risk factors allows providers to discuss potential postoperative ECMO candidacy at the preoperative visit, improving prognosis clarity to both patients and their families.

4.2 | Cardiac surgical volume

We demonstrated that ACHD patients undergoing surgery at medium and low volume hospitals were at increased risk for DWE vs ECMO when compared to patients undergoing surgery at high-volume ACHD surgical programs based at children's hospitals. A previous study of pediatric cardiac surgical centers demonstrated that lower volume pediatric surgical centers use ECMO less frequently than higher volume centers.[29] However, additional pediatric data from Mascio et al did not report a clear association between pediatric cardiac surgical volume and adjusted ECMO rate.[10] Detailed data regarding this comparison from adult hospitals is not available. Increased ECMO use by higher volume centers could be a potential mechanism by which higher volume centers achieve lower mortality rates.

Adults may receive their congenital heart care at pediatric or adult hospitals; it is important for them to understand the risks and complications of any procedures they may undergo. Since ECMO is a commonly available support modality after adult congenital heart disease surgery, discussion of this and other possible mechanical circulatory support should occur before surgery. This study provides information that physicians and surgeons can use to counsel their patients about outcomes as well as risks after ACHD surgery.

This analysis has limitations inherent in a retrospective analysis of administrative data, including lack of physiological data. While granular clinical data is not available in PHIS, we attempted to reconstruct the delivery of care based on diagnosis and procedure codes. This analysis only evaluated the surgeries performed at children's hospitals and did not include similar surgeries performed at adult hospitals due to the nature of the database. Additionally, there were a relatively low number of clinical outcomes of interest, limiting the comparisons that can be made. Finally, we did not evaluate other possible methods of postoperative mechanical support as these are uncommon in children's hospitals overall.

5 | CONCLUSION

We have shown that there are similar but distinct risk factors for ECMO and DWE after ACHD surgery. Understanding the differences between the predictors of the two outcomes can improve clinical care and helps physicians understand our current clinical practice. Additionally, this information can be used to provide anticipatory guidance to patients and their families during presurgical counseling.

CONFLICT OF INTEREST

Dr Bratton disclosed that she served on the American Board of Pediatrics (ABP) as the immediate past chair through 2016. Dr Thiagarajan's institution received funding from Bristol Myers Squibb (Events Adjudication Committee) and from Pfizer (Events Adjudication Committee). The remaining authors have disclosed that they do not have any potential conflicts of interest.

AUTHOR CONTRIBUTIONS

SJD: Concept/design, data analysis/interpretation, drafting article, critical revision of article, statistics, approval of article.
EVK: Data analysis/interpretation, critical revision of article, approval of article.
JW: Data analysis/interpretation, critical revision of article, data management, approval of article.
SLB: Data analysis/interpretation, critical revision of article, approval of article.
RRT: Data analysis/interpretation, critical revision of article, approval of article.
CSB: Concept/design, data analysis/interpretation, critical revision of article, approval of article.
TC: Concept/design, data analysis/interpretation, critical revision of article, statistics, approval of article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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