Supplemental Digital Content

The Association Between Vasopressin and Adverse Kidney Outcomes in Children and Young Adults Requiring Vasopressors on Continuous Renal Replacement Therapy

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Supplemental Methods

VA exposure was quantified by the fraction of total vasoactive load (by VIS) contributed by VA each day:

*%VIS VA= [10*VA (mU/kg/min)/(VIS)]x100*

To characterize the trend in VIS each day of CRRT, for each patient we calculated a daily percent change in VIS using the formula: *%Change VIS= [(VIS CRRT Day (n+1)/VIS CRRT Day n)–1]x100.*

For patients with VIS CRRT Day (n+1)= 0 (i.e., they are now off vasoactives but were on the day prior), -100% was imputed; for patients with VIS CRRT Day n=0 (i.e., they are now on vasoactives but were not the day prior), +100% was imputed.

Percent fluid balance from ICU admission to CRRT initiation was calculated using the standard formula:

%Fluid Balance= [(Total fluid in (mL–Total fluid out (mL))/ICU admit weight (kg)]x100

Supplemental Tables:

Supplemental Table 1: Comparison of daily vasoactive inotropic score (VIS) for each day of CRRT in children who received vasopressin (VA Group) versus those who did not (No VA Group) and fraction of daily VIS from vasopressin in VA Group patients.

CRRT Day	No VA Group VIS N=417	VA Group VIS N=248	*p*	%Daily VIS from VA
0	7 (2, 20)	19 (8, 39)	<0.001	18 (3, 37)
1	5 (0, 15)	16 (5, 32)	<0.001	19 (0, 39)
2	3 (0, 10)	10 (2, 23)	<0.001	17 (0, 41)
3	2 (0, 7)	7 (1, 21)	<0.001	19 (0, 46)
4	0 (0, 6)	6 (0, 18)	<0.001	17 (0, 50)
5	0 (0, 6)	4 (0, 13)	<0.001	2 (0, 55)
6	0 (0, 5)	4 (0, 14)	<0.001	0 (0, 60)
7	0 (0, 5)	3 (0, 12)	0.013	13 (0, 56)

Continuous variables presented as median (IQR). CRRT- continuous renal replacement therapy; VA-vasopressin; VIS- vasoactive-inotropic score

Supplemental Table 2: Demographic, clinical characteristics, and outcomes of children with sepsis requiring vasopressors while receiving continuous renal replacement therapy (CRRT) who received vasopressin compared to those who did not.

Variable	All (n=343)	No VA (n= 197)	VA (n= 146)	*p*
Demographics				
Age, years	10 (2.3,15.3)	8.8 (2,15)	10.5 (2.5,15.6)	0.62
Sex				
Female (%)	162 (47)	91 (46)	71 (49)	0.66
Male (%)	181 (53)	106 (54)	75 (51)	
Admission weight, kg	31 (13,58)	28 (13,57)	33 (13,59)	0.49
Admission Diagnosis, n (%)				0.92
Shock/Infection/Major Trauma	200 (58)	111 (56)	89 (61)	
Respiratory Failure	67 (20)	39 (20)	28 (19)	
CNS Dysfunction	13 (4)	9 (5)	4 (3)	
Post-surgical/Minor Trauma	11 (3)	5 (3)	6 (4)	
Primary Cardiac	25 (7)	15 (8)	10 (7)	
Other	27 (8)	18 (9)	9 (6)	
Comorbidities, n (%)				0.58
0	65 (19)	36 (18)	29 (20)	
1	158 (46)	88 (45)	70 (48)	
2	71 (21)	46 (23)	25 (17)	
>2	49 (14)	27 (14)	22 (15)	
PRISM III	16 (11,20)	15 (11,19)	16 (12,22)	0.06
CRRT Initiation Data				
Time from ICU Admission to CRRT, days	2 (1,7)	2 (1,6)	2 (1,8)	0.95
PELOD-2	7 (4,10)	7 (4,9)	8 (4,11)	0.041
Receipt of Vasopressors, n (%)	286 (84)	152 (78)	134 (92)	<0.001
Pre-CRRT VIS	15 (5,38)	10 (3,27)	28 (12,47)	<0.001
Mechanical Ventilation, n (%)	331 (97)	189 (96)	142 (97)	0.51
Urine Output 24 hours Prior, ml/kg/hr	0.4 (0.13,1.2)	0.5 (0.14,1.3)	0.36 (0.1,1)	0.11
Time to First Negative Fluid Balance, days	1 (0,1)	1 (0,1)	1 (0,1)	0.44
Outcomes				
28-day CRRT Liberation Status, n (%)				0.02
Liberated	94 (27)	65 (33)	29 (20)	
Liberation not attempted	162 (47)	83 (42)	79 (54)	
Reinstituted	87 (25)	49 (25)	28 (26)	
CRRT Duration, days	7 (4,16)	7 (4,16)	7 (3,16)	0.38
%Day 1-7 of CRRT Requiring Vasopressors	83 (43,100)	63 (36,100)	100 (62,100)	<0.001
28-day Ventilator-Free Days	0 (0,23)	2 (0,28)	0 (0,20)	0.005
28-day ICU-Free Days	0 (0,2)	0 (0,7)	0 (0,0)	0.001
In-Hospital Mortality, n (%)	162 (47)	105 (53)	89 (61)	0.009
MAKE-90, n (%)	248 (73)	128 (66)	120 (82)	0.001
90-day mortality, n (%)	181 (53)	92 (47)	89 (61)	0.009
Persistent kidney dysfunction, n (%)	53 (15)	28 (14)	25 (17)	0.46
RRT dependence, n (%)	14 (4)	8 (4)	6 (4)	0.98

The VA Group consisted of all patients who received vasopressin and/or norepinephrine/epinephrine, while the No VA Group consisted of patients receiving norepinephrine/epinephrine without vasopressin. Continuous variables reported as median (IQR). *p*-values were obtained using Pearson's Chi-squared test, Wilcoxon rank sum test, or Fisher's Exact Test, as appropriate. CNS- central nervous system; PRISM III- Pediatric Risk of Mortality III score; PELOD-2- Pediatric Logistic Organ Dysfunction 2 score; VIS- vasoactive-inotropic score; CRRT- continuous renal replacement therapy

Supplemental Table 3: Demographic, clinical characteristics, and outcomes of children who initiated continuous renal replacement therapy (CRRT) ≤2 days from admission and required vasopressors who received vasopressin compared to those who did not.

Variable	All (n=342)	No VA (n=217)	VA (n=125)	*p*
Demographics				
Age, years	8.3 (1.7, 14.9)	6 (1.2,14.5)	10.3 (2.7,15.8)	0.07
Sex				0.12
Female (%)	150 (44)	102 (47)	48 (38)	
Male (%)	192 (46)	115 (53)	77 (62)	
Admission weight, kg	25 (12,59)	21 (11,60)	34 (14,58)	0.09
Admission Diagnosis, n (%)				0.038
Shock/Infection/Major Trauma	161 (47)	88 (41)	73 (58)	
Respiratory Failure	65 (19)	45 (21)	20 (16)	
CNS Dysfunction	17 (5)	14 (7)	3 (2)	
Post-surgical/Minor Trauma	14 (4)	8 (4)	6 (5)	
Primary Cardiac	32 (9)	23 (10)	9 (1)	
Other	53 (16)	39 (18)	14 (11)	
Comorbidities, n (%)				0.33
0	65 (19)	40 (18)	25 (20)	
1	167 (49)	100 (46)	67 (54)	
2	78 (23)	56 (26)	22 (18)	
>2	32 (9)	21 (10)	11 (9)	
PRISM III	16 (12,21)	16 (12,20)	26 (14,23)	0.04
Sepsis, n (%)	189 (55)	106 (49)	83 (66)	0.002
CRRT Initiation Data				
Time from ICU Admission to CRRT, days	1 (0,2)	1 (1,2)	1 (1,2)	0.83
PELOD-2	7 (4,10)	7 (4,9)	8 (5,10)	0.021
Receipt of Vasopressors, n (%)	274 (80)	159 (73)	115 (92)	<0.001
Pre-CRRT VIS	16 (4,36)	10 (0,27)	28 (13,47)	<0.001
Mechanical Ventilation, n (%)	322 (94)	204 (94)	118 (95)	0.66
Urine Output 24 hours Prior, ml/kg/hr	0.35 (0.1,0.98)	0.3 (0.1,1.2)	0.3 (0.1,0.88)	0.32
Time to First Negative Fluid Balance, days	1 (0.2)	1 (0,2)	1 (0,20)	0.53
Outcomes				
28-day CRRT Liberation Status, n (%)				0.031
Liberated	102 (30)	75 (35)	27 (22)	
Liberation not attempted	155 (45)	89 (41)	66 (53)	
Reinstituted	85 (25)	53 (24)	32 (26)	
CRRT Duration, days	7 (3,15)	7 (3,14)	6 (2,16)	0.60
%Day 1-7 of CRRT Requiring Vasopressors	75 (40,100)	63 (38,100)	100 (63,100)	<0.001
28-day Ventilator-Free Days	4 (0,28)	14 (0,28)	0 (0,21)	0.011
28-day ICU-Free Days	0 (0,10)	0 (0,12)	0 (0,5)	0.004
In-Hospital Mortality, n (%)	160 (47)	93 (43)	67 (54)	0.06
MAKE-90, n (%)	234 (70)	137 (65)	97 (78)	0.017
90-day mortality, n (%)	158 (46)	92 (42)	66 (53)	0.06
Persistent kidney dysfunction, n (%)	54 (16)	29 (13)	25 (20)	0.11
RRT dependence, n (%)	22 (6)	16 (4)	6 (5)	0.35

The VA Group consisted of all patients who received vasopressin and/or norepinephrine/epinephrine, while the No VA Group consisted of patients receiving norepinephrine/epinephrine without vasopressin. Continuous variables reported as median (IQR). *p*-values were obtained using Pearson's Chi-squared test, Wilcoxon rank sum test, or Fisher's Exact Test, as appropriate. CNS- central nervous system; PRISM III- Pediatric Risk of Mortality III score; PELOD-2- Pediatric Logistic Organ Dysfunction 2 score; VIS- vasoactive-inotropic score; CRRT- continuous renal replacement therapy

Supplemental Table 4: Comparison of median percent change in vasoactive inotropic score (VIS) for each day of CRRT by timing of vasopressin administration in patients receiving vasopressin (VA Group)

%Change VIS by CRRT Day	N	Early VA	Intermediate VA	Late VA	*p*
Day 1	199	-18 (-55, 0)	100 (31, 188)	-13 (-92, 75)	<0.001
Day 2	165	-25 (-69, 0)	10 (-34, 100)	0 (-54, 79)	<0.001
Day 3	132	-23 (-74, 0)	-10 (-28, 10)	100 (72, 121)	<0.001
Day 4	108	-32 (-64, 0)	-3 (-46, 18)	10 (-23, 100)	0.024
Day 5	91	-4 (-52, 40)	0 (-35, 20)	-40 (-74, 0)	0.299
Day 6	75	-14 (-67, 43)	19 (-37, 53)	40 (-29, 100)	0.136
Day 7	64	-7 (-66, 18)	0 (-32, 7)	10 (0, 90)	0.163

Continuous variables reported as median (IQR). Comparisons made via Kruskall-Wallis test. VIS-vasoactive inotropic score; CRRT-continuous renal replacement therapy; VA-vasopressin.

Supplemental Table 5: Demographic, clinical characteristics, and outcomes of children with vasodilatory shock receiving CRRT who survived until Day 7 of CRRT *or* successfully liberated from CRRT by Day 7 based on timing of vasopressin administration (sensitivity analysis cohort)

Variable	Early VA (n=110)	Intermediate VA (n=28)	Late VA (n=23)	*p*
Demographics				
Age, years	10.4 (2.8, 15.6)	4.7 (1.2, 14.6)	10.8 (1.3, 14.5)	0.37
Sex, Female (%)	49 (45)	12 (43)	13 (57)	0.54
Male (%)	61 (55)	16 (57)	10 (43)	
Admission weight, kg	31 (14, 65)	20 (12, 47)	38 (10, 51)	0.26
Admission Diagnosis, n (%)				0.17
Shock/Infection/Major Trauma	54 (49)	11 (39)	6 (26)	
Respiratory Failure	20 (18)	7 (25)	7 (30)	
Post-surgical/Minor Trauma	5 (4.5)	3 (11)	1 (4.3)	
Primary Cardiac	20 (18)	3 (11)	6 (26)	
Other	11 (10)	4 (15)	3 (13)	
Comorbidities, n (%)				0.22
0	24 (22)	4 (14)	3 (13)	
1	55 (50)	15 (54)	8 (35)	
2	17 (15)	4 (14)	9 (39)	
>2	14 (13)	5 (18)	3 (13)	
PRISM III	16 (12, 20)	15 (8, 19)	13 (10, 18)	0.25
Sepsis, n (%)	62 (56)	14 (50)	12 (52)	0.81
CRRT Initiation Data				
Time from ICU Admission to CRRT, days	2 (1, 9)	4 (2, 13)	6 (3, 11)	0.13
PELOD-2	7.0 (4.3, 10.0)	7.0 (3.8, 8.3)	6.0 (3.5, 10.5)	0.75
Receipt of Vasopressors, n (%)	105 (95%)	22 (79%)	18 (78%)	0.002
Pre-CRRT VIS	29 (14, 40)	10 (2, 21)	5 (2, 15)	<0.001
Mechanical Ventilation, n (%)	107 (97%)	27 (96%)	23 (100%)	>0.99
%Fluid Balance from ICU Admission	11 (5, 27)	11 (5, 24)	13 (4, 25)	0.93
Urine Output 24 hours Prior, ml/kg/hr	0.40 (0.15, 0.98)	0.42 (0.19, 0.93)	0.63 (0.32, 1.26)	0.50
Time to First Negative Fluid Balance, days	1.00 (0.0, 2.0)	1.00 (0.0, 2.0)	1.00 (0.0, 1.0)	0.39
Outcomes				
28-day CRRT Liberation Status, n (%)				0.003
Liberated	40 (36)	8 (29)	5 (22)	
Liberation not attempted	25 (23)	16 (57)	11 (48)	
Reinstituted	45 (41)	4 (14)	7 (30)	
CRRT Duration, days	12 (6, 21)	16 (10, 50)	13 (8, 20)	0.055
%Day 1-7 of CRRT Requiring Vasopressors	83 (50, 100)	100 (75, 100)	88 (63, 88)	0.24
28-day Ventilator-Free Days	16 (0, 28)	0 (0, 14)	1 (0, 22)	0.022
28-day ICU-Free Days	0 (0, 7.8)	0 (0, 0)	0 (0, 0)	0.006
In-Hospital Mortality, n (%)	34 (31)	13 (46)	11 (48)	0.14
MAKE-90, n (%)	68 (62)	24 (86)	18 (78)	0.029
90-day mortality, n (%)	30 (27)	14 (50)	11 (48)	0.025
Persistent kidney dysfunction, n (%)	30 (27)	4 (14)	5 (22)	0.34
RRT dependence, n (%)	8 (7)	6 (21)	2 (9)	0.08

Early VA Group initiated VA on Day 0 of CRRT, Intermediated VA Group initiated VA on Day 1-2 of CRRT, and Late VA Group initiated VA on Days 3-7 of CRRT. Continuous variables reported as median (IQR). *p*-values were obtained using Pearson's Chi-squared test, Wilcoxon rank sum test, or Fisher's Exact Test, as appropriate. VA-vasopressin; CNS- central nervous system; PRISM III- Pediatric Risk of Mortality III score; PELOD-2- Pediatric Logistic Organ Dysfunction 2 score; VIS- vasoactive-inotropic score; CRRT- continuous renal replacement therapy

Supplemental Table 6: Comparison of median daily percent change in vasoactive inotropic score (VIS) for each day of CRRT by timing of vasopressin administration in patients receiving vasopressin who survived until Day 7 of CRRT *or* successfully liberated from CRRT by Day 7 (sensitivity analysis cohort)

%Change VIS by CRRT Day	N	Early VA	Intermediate VA	Late VA	*p*
Day 1	142	-27 (-64, 0)	100 (10, 192)	-13 (-100, 5)	<0.001
Day 2	126	-33 (-68, 0)	-10 (-63, 100)	-23 (-58, 75)	0.16
Day 3	108	-33 (-77, 0)	-11 (-27, 16)	100 (69, 104)	<0.001
Day 4	94	-38 (-67, 0)	-13 (-47, 17)	0 (-45, 62)	0.30
Day 5	82	-7 (-52, 40)	-9 (-40, 10)	-28 (-55, 0)	0.60
Day 6	73	-14 (-67, 43)	25 (-37, 55)	35 (-30, 100)	0.20
Day 7	64	-7 (-66, 18)	0 (-32, 7)	10 (0, 90)	0.16

Continuous variables reported as median (IQR). Comparisons made via Kruskall-Wallis test. VIS-vasoactive inotropic score, CRRT-continuous renal replacement therapy, VA-vasopressin

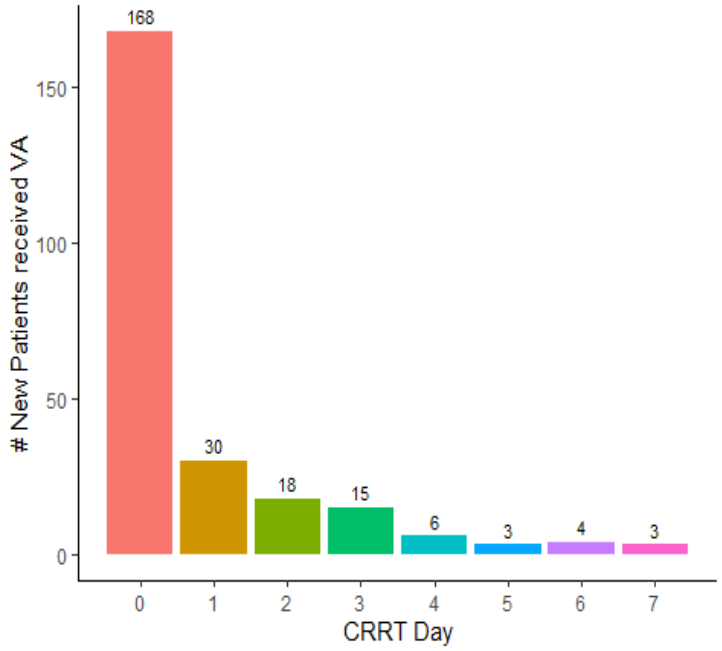
Supplemental Table 7: Multivariable analyses examining the association between *a priori* selected demographic and clinical variables and the primary outcomes of successful CRRT liberation and development of MAKE-90 in patients receiving vasopressin who survived until Day 7 of CRRT *or* successfully liberated from CRRT by Day 7 (sensitivity analysis cohort)

Variable	aOR Liberation Success	95% CI	*p*	aOR MAKE-90	95% CI	*p*
Timing of VA Initiation Early Intermediate/Late	1.60	0.58, 4.43	0.37	2.54	1.07, 6.02	0.035
Pre-CRRT PELOD-2	0.97	0.88, 1.07	0.55	1.05	0.96, 1.14	0.29
Pre-CRRT VIS	1.01	0.99, 1.03	0.23	1.00	0.98, 1.01	0.54
Pre-CRRT UOP, ml/kg/hr	1.45	0.85, 2.50	0.18	0.96	0.61, 1.52	0.87
Comorbidities, yes	0.65	0.23, 1.81	0.41	2.19	0.93, 5.16	0.072

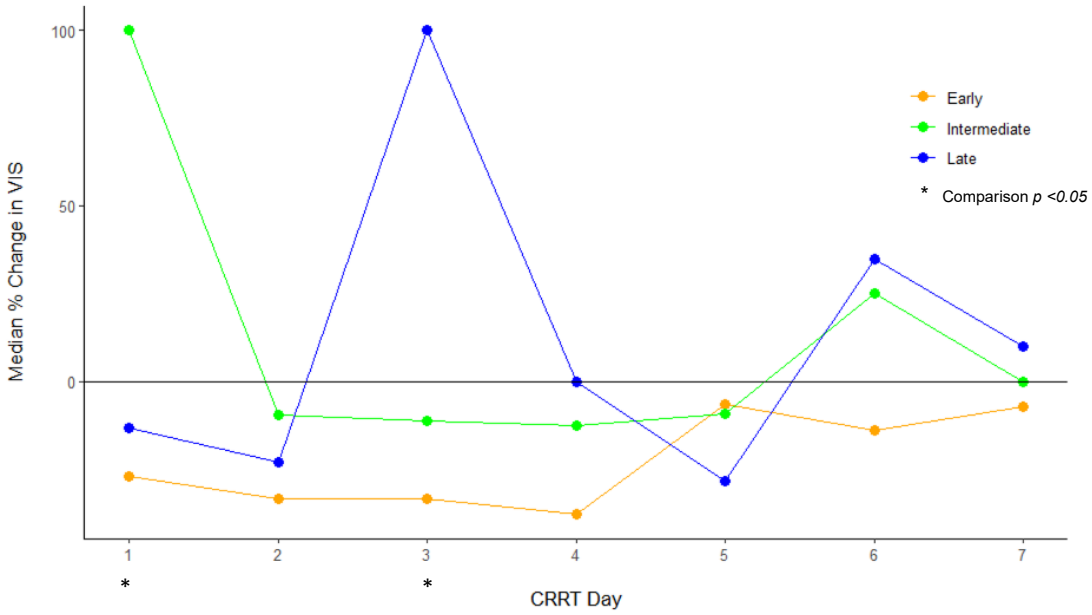
Multivariable logistic regression performed with above *a priori* selected variables using mixed-effects logistic regression to adjust for center. VA-vasopressin; UOP-urine output; PELOD-2-Pediatric Logistic Organ Dysfunction 2 score; VIS-vasoactive-inotropic score; CRRT-continuous renal replacement therapy

Supplemental Figures:

Supplemental Figure 1: Histogram of timing of vasopressin initiation in patients who received vasopressin (VA Group). VA-vasopressin; CRRT-continuous renal replacement therapy.



Supplemental Figure 2: Median daily percent change in vasoactive inotropic score (VIS) by timing of vasopressin initiation (Early, Intermediate, or Late) in patients receiving vasopressin who survived until Day 7 of CRRT *or* successfully liberated from CRRT by Day 7 (sensitivity analysis cohort). * represents statistical significance. VIS-vasoactive inotropic score; CRRT-continuous renal replacement therapy.



SUPPLEMENTARY APPENDIX 1: Institutional Review Board (IRB) Information for Each WE-ROCK Site

	Site (City)	Country/State	Principal Investigator(s)	IRB Board Name	IRB #	Approval Date
1	Kings College (London)	United Kingdom	Akash Deep	Information Governance Department	310522DTA/KCH/Cincinnati	5/17/2022
2	Bambino Gesu Children's Hospital	Italy	Gabriella Bottari Valeria Raggi	Bambino Gesu Children's Hospital Ethics Committee	n869 n870	6/21/2022
3	Meyer Children Hospital (Florence)	Italy	Zaccaria Ricci	Comitato Etico Pediatrico, Florence Italy	32/2022	2/15/2022
4	Gregorio Marañón University Hospital (Madrid)	Spain	Sarah Fernandez LaFever	Comité de Ética de la Investigación con Medicamentos Hospital General Universitario Gregorio Marañón	Dict_69_22	12/13/2022
5	Medical University (Innsbruck)	Austria	Gerard Cortina	Ethics Commission of the Medical University of Innsbruck	1225/2022	8/25/2022
6	Royal Children's Hospital (Melbourne)	Australia	Ben Gelbart	Royal Children's Hospital Melbourne Human Research Ethics Committee	HREC Reference Number: HREC/84977/RCHM-2022 RCH HREC Reference Number: 84977	6/3/2022
7	Hospital for Sick Children (Toronto)	Canada	Michael Zappitelli	The Hospital for Sick Children	1000078866	11/8/2021
8	Stollery Children's Hospital (Edmonton)	Canada	Rashid Alobaidi	University of Alberta Research Ethics Board	Pro00117369	1/24/2022
9	Sidra Medicine (Doha)	Qatar	Ahmad Kaddourah	Sidra IRB MOPH	1979858	3/9/2023
10	Osaka Municipal General Medical Center (Osaka City)	Japan	Taiki Haga	Osaka Municipal General Medical Center, Administrative Agency	2302135	8/8/2023
11	Cincinnati Children's Hospital (Cincinnati)	Ohio	Katja Gist	Cincinnati Children's Hospital IRB	2021-0265	7/31/2021
12	Seattle Children's Hospital (Seattle)	Washington	Shina Menon	Seattle Children's Hospital IRB	STUDY00002682	5/24/2021
13	Stanford Children's Hospital (Palo Alto)	California	Michaela Damian	Stanford University IRB	#63289	11/29/2021
14	Mattel Children's Hospital (Los Angeles)	California	Rachana Srivastava	University of California Los Angeles IRB	#22-000626	4/26/2022
15	Children's Hospital Colorado (Aurora)	Colorado	Erin Stenson	Colorado Multiple IRB	COMIRB19-1788	4/9/2021

16	Mercy Children's Hospital (Kansas City)	Kansas	Kristin Dolan	Children's Mercy IRB	STUDY00002178	2/8/2022
17	St Louis Children's Hospital (St. Louis)	Missouri	Tara Neumyr	Washington University IRB	202111077	11/15/2021
18	University of Iowa Stead Family Children's Hospital (Iowa City)	Iowa	Amy Strong	University of Iowa Human Subjects Office/IRB	#202109447	10/8/2021
19	Texas Children's Hospital (Houston)	Texas	Sameer Thadani	Baylor College of Medicine	H-32217	11/29/2021
20	Nationwide Children's Hospital (Columbus)	Ohio	Aimee Bigelow	Nationwide Children's Hospital IRB	STUDY0002103	9/10/2021
21	Children's Hospital of Pittsburgh (Pittsburgh)	Pennsylvania	Dana Fuhrman	University of Pittsburgh IRB	#21040198	5/18/2021
22	Riley Children's Hospital (Indianapolis)	Indiana	Michelle Starr	Indiana University HRPP	#12121	7/9/2021
23	University of Minnesota Children's Hospital (Minneapolis)	Minnesota	Shanti Balani	University of Minnesota	#00015246	3/4/2022
24	C.S. Mott Children's Hospital (Ann Arbor)	Michigan	Stephen Gorga	University of Michigan	HUM00206428	12/25/2021
25	Children's National (Washington, DC)	--	Aadil Kakajiwala	Children's National IRB	Pro00016977	12/26/2021
26	Maria Fareri Children's Hospital at Westchester Medical Center (Valhalla)	New York	Sonia Solomon	New York Medical College IRB	#14813	03/23/2022
27	Cohen Children's Medical Center (New Hyde Park)	New York	Abby Basalely	Feinstein Institute of Medical Research Northwell Health IRB	21-1250	11/23/2021
28	Lurie Children's Hospital (Chicago)	Illinois	Theresa Mottes	Lurie Children's IRB	2022-4905	11/15/2021
29	LeBonheur Children's Hospital (Memphis)	Tennessee	Pilar Anton-Martin	LeBonheur IRB	21-08548-XM	1/10/2022
30	Medical University of South Carolina (Charleston)	South Carolina	David Selewski	MUSC IRB	Pro00114501	9/30/2021
31	Children's of Alabama (Birmingham)	Alabama	Tennille Webb	University of Alabama at Birmingham IRB	300008197	10/20/2021
32	Children's Healthcare of Atlanta (Atlanta)	Georgia	Stella Shin	Children's Healthcare of Atlanta IRB	STUDY00001129	7/28/2021
33	Omaha Children's Hospital (Omaha)	Nebraska	Melissa Muff-Luett	University of Nebraska Medical Center IRB	0100-22-EP	5/20/2022
34	Golisano Children's Hospital (Rochester)	New York	Susan Martin	Rochester Subject Review Board at the University of Rochester	STUDY00006703	12/13/2021

SUPPLEMENTARY APPENDIX 2:

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1,6
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8
Objectives	3	State specific objectives, including any prespecified hypotheses	8-9
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-11
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	12
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	12

		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12-14
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14, 16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2