Risk factors for functional decline and impaired quality of life after pediatric respiratory failure

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ONLINE DATA SUPPLEMENT

RESTORE Investigators

Figure E1. Flow diagram of study patients enrolled in the *RESTORE* (Randomized Evaluation of Sedation Titration for Respiratory Failure) trial, including follow-up

Table E1. ITQOL scores at 6 months post-discharge according to functional status at baseline

Table E2. Factors present at admission and hospital course variables according to impaired HRQL based on ITQOL growth and development score in patients with normal functional status at baseline

Table E3. PedsQL scores at 6 months post-discharge according to functional status at baseline

Table E4. Factors present at admission and hospital course variables according to impaired HRQL based on PedsQL total score in patients with normal functional status at baseline

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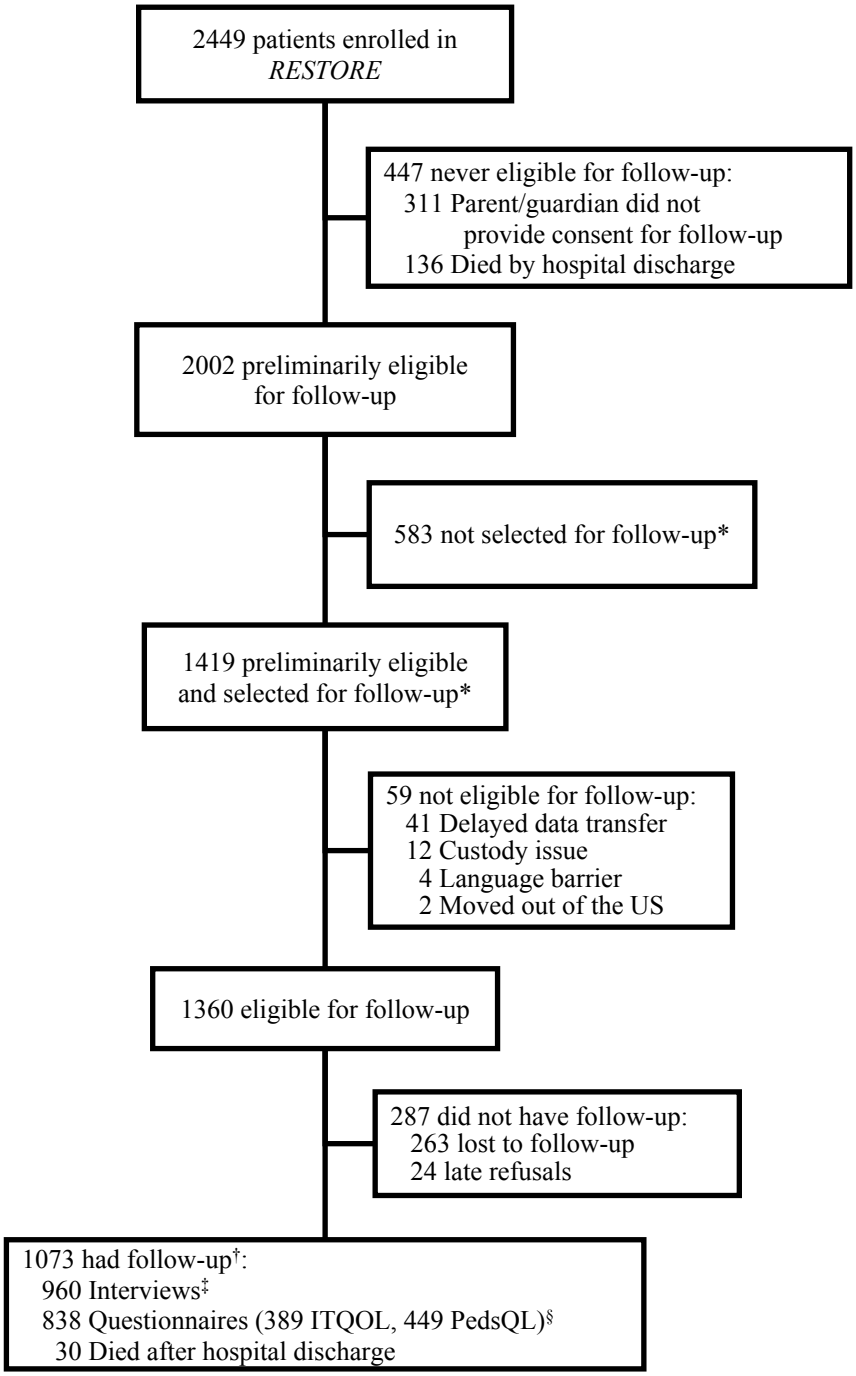

Figure E1. Flow diagram of study patients enrolled in the *RESTORE* trial, including follow-up.
RESTORE=Randomized Evaluation of Sedation Titration for Respiratory Failure. ITQOL=Infant and Toddler Quality of Life Questionnaire. PedsQL=Pediatric Quality of Life Inventory.
* Patients were randomly selected for post-discharge assessments, stratified by age group (<2, 2-4, 5-7, 8-12, and 13-18 years) and site. Comparing patients selected vs. not selected for follow-up, there were no differences in normal functional status at baseline (73% vs. 74%; *P*=0.75) or hospital discharge (66% vs. 67%; *P*=0.76).
† Follow-up rate: 1073/1360 = 79%.

‡ Of the 960 patients whose parents/guardians completed follow-up interviews including assessment of functional status, 960 patients had functional status data at baseline and 946 at hospital discharge.
§ Parents/guardians provided health-related quality of life data via ITQOL or PedsQL. For ITQOL, parents/guardians provided data for 53 patients 6 years of age or older; these data were excluded, as the instrument is validated for children younger than 6 years of age. For PedsQL, parents/guardians provided incomplete data for five patients, so that the PedsQL could not be scored.

Table E1. ITQOL scores at 6 months post-hospital discharge according to functional status at baseline

Variable	Normal function* (n = 273)	Impaired function* (n = 63)	US norms[E1] (n = 1443)	*P* value normal vs US norms†	*P* value impaired vs US norms†
Age at ITQOL, *n* (%)					
<1 y	128 (47)	10 (16)			
1 to <2 y	132 (48)	33 (52)			
2 to <6 y	13 (5)	20 (32)			
ITQOL scores, mean (SD)‡,§					
Overall health	78.0 (22.3)	58.1 (26.0)			
Physical abilities	87.4 (25.3)	60.8 (33.1)	96.3 (15.7)	0.0001	<0.0001
Growth and development	89.2 (15.3)	65.4 (22.2)	93.1 (12.5)	<0.0001	<0.0001
Bodily pain and discomfort	78.1 (20.2)	75.8 (22.5)	85.2 (16.1)	<0.0001	<0.0001
Temperament and moods	81.0 (12.1)	75.4 (14.1)	80.3 (11.8)	0.33	0.008
General behavior‖	77.5 (15.0)	76.1 (15.0)	72.3 (16.1)	<0.0001	0.06
Global behavior‖	82.7 (20.7)	82.1 (23.3)			
Getting along with others‖	72.7 (11.6)	66.1 (14.2)	74.9 (11.7)	0.03	<0.0001
General health perceptions	50.1 (16.9)	35.4 (17.8)	78.9 (13.1)	<0.0001	<0.0001
Change in health compared to 1 year ago, *n* (%)‖					
Much better now	69 (49)	24 (47)			
Somewhat better now	23 (16)	13 (25)			
About the same now	36 (26)	10 (20)			
Somewhat worse now	9 (6)	2 (4)			
Much worse now	3 (2)	2 (4)			

ITQOL=Infant and Toddler Quality of Life Questionnaire, from patients <2 years old or 2-6 years old with substantial developmental impairment. SD=standard deviation.

* Normal functional status at baseline is defined as Pediatric Cerebral Performance Category (PCPC) = 1 and Pediatric Overall Performance Category (POPC) = 1, while impaired functional status is defined as POPC>1.

† *P* values comparing functional group mean scores with reference population means were calculated using linear regression accounting for pediatric intensive care unit as a cluster variable using generalized estimating equations.

‡ Higher scores indicate better health-related quality of life.

§ Missing less than 8% of ITQOL scores in the normal and impaired function groups.

‖ Assessed in children 1 y of age and older.

Table E2. Factors present at admission and hospital course variables according to impaired HRQL based on ITQOL growth and development score in patients with normal functional status at baseline

Variable	Not impaired HRQL (n = 216)	Impaired HRQL (n = 55)	*P* value unadj*	*P* value adj†
Factors present at hospital admission				
Sociodemographic factors and pre-existing health status				
Age at ITQOL, *n* (%)			0.66	
<1 y	104 (48)	23 (42)		
1 to <2 y	102 (47)	29 (53)		
2 to <6 y	10 (5)	3 (5)		
Female, *n* (%)	89 (41)	25 (45)	0.52	
Non-Hispanic white, *n*/total (%)	134/215 (62)	32/55 (58)	0.23	
Parent education, *n* (%)			0.007	
Some high school	21 (13)	8 (18)		
High school graduate/G.E.D.	32 (20)	15 (33)		
Some college or technical school	52 (33)	10 (22)		
College graduate/postgraduate	55 (34)	12 (27)		
Unknown, *n*	56	10		
Median household income of zip code of residence, *n* (%)‡			0.68	
<$40,000	41 (19)	11 (20)		
$40,000-$79,999	132 (61)	35 (64)		
≥$80,000	43 (20)	9 (16)		
Any medical history, *n* (%)				
Prematurity (<36 wk postmenstrual age)	35 (16)	13 (24)	0.29	
Asthma (prescribed bronchodilators or steroids)	8 (4)	1 (2)	0.40	
Cancer (current or previous diagnosis)	4 (2)	1 (2)	0.98	
Features of the presentation of acute illness				
PRISM III-12 score, median (IQR)§	5 (2-8)	3 (1-8)	0.92	
Risk of mortality based on PRISM III-12 score, median (IQR), %	1.7 (0.7-4.8)	1.3 (0.7-4.9)	0.67	
Primary diagnosis category, *n* (%)			0.02	
Bronchiolitis or asthma (or reactive airway disease)	136 (63)	28 (51)		
Pneumonia or aspiration pneumonia	52 (24)	14 (25)		
Acute respiratory failure related to sepsis	12 (6)	5 (9)		
Other acute diagnoses‖	14 (6)	5 (9)		
Other chronic diagnoses‖	2 (<1)	3 (5)		
Hospital course variables				
Moderate/severe PARDS based on worst OI or OSI during hospitalization, *n* (%)¶	148 (69)	41 (75)	0.28	0.27
Early NMB (for the entire duration of days 1 and 2), *n* (%)	24 (11)	5 (9)	0.55	0.55
HFOV, *n* (%)	29 (13)	5 (9)	0.46	0.46
ECMO, *n* (%)	8 (4)	0	0.37**	-
Non-invasive ventilation prior to intubation, *n* (%)	90 (42)	24 (44)	0.87	0.82
Non-invasive ventilation post-extubation, *n* (%)	97 (45)	24 (44)	0.79	0.84
Duration of mechanical ventilation, median (IQR), d	6.5 (4.0-9.6)	7.2 (4.3-11.0)	0.21	0.28
<7 d, *n* (%)	119 (55)	27 (49)	0.57	0.59
7 to <14 d	73 (34)	21 (38)		
14 to <28 d	20 (9)	5 (9)		
≥28 d (including transfers by day 28)	4 (2)	2 (4)		
MODS (concurrent or new), *n* (%)††	136 (63)	33 (60)	0.72	0.72
Extrapulmonary organ dysfunction during hospitalization, *n* (%)				
Cardiovascular	69 (32)	18 (33)	0.93	0.89
Neurologic	97 (45)	25 (45)	0.78	0.90
Hematologic	19 (9)	6 (11)	0.56	0.52
Renal	7 (3)	1 (2)	0.63	0.60
Hepatic	20 (9)	9 (16)	0.13	0.14
Number of organ dysfunctions, median (IQR)	2 (1-2)	2 (1-3)	0.49	0.54
Mean daily opioid dose, median (IQR), mg/kg	1.5 (0.6-2.5)	1.5 (0.8-3.4)	0.50	0.58
Mean daily benzodiazepine dose, median (IQR), mg/kg	1.3 (0.6-2.4)	1.9 (0.8-3.1)	0.36	0.45
Synthetic primary opioid agent, *n* (%)‡‡	89 (41)	24 (44)	0.70	0.79
Dexmedetomidine, *n* (%)	73 (34)	15 (27)	0.29	0.19
Clonidine, *n* (%)	25 (12)	9 (16)	0.30	0.40
Ketamine, *n* (%)	38 (18)	13 (24)	0.11	0.16
Barbiturates, *n* (%)	26 (12)	8 (15)	0.56	0.67

Methadone, *n* (%)	39 (18)	18 (33)	0.03	0.03
Antidelirium medication, *n* (%)	1 (<1)	0	>0.99**	-
≥4 sedative classes, *n* (%)§§	51 (24)	17 (31)	0.13	0.11
Study days awake and calm (daily modal SBS score -1 or 0), median (IQR), %	86 (67-100)	85 (67-100)	0.68	0.81
Heavy sedation (daily modal SBS score ever -3), *n* (%)	22 (10)	6 (11)	0.72	0.82
Inadequate pain management, *n* (%)‖‖	26 (12)	14 (25)	0.005	0.005
Inadequate sedation management, *n* (%)‖‖	54 (25)	12 (22)	0.73	0.65
Clinically significant iatrogenic withdrawal, *n* (%)¶¶	26 (12)	10 (18)	0.14	0.17
Length of stay				
PICU, median (IQR), d	8.8 (5.8-13.8)	9.7 (6.1-16.4)	0.02	0.03
<7 d, *n* (%)	73 (34)	18 (33)	0.09	0.11
7 to <14 d	91 (42)	19 (35)		
14 to <28 d	42 (19)	11 (20)		
≥28 d	10 (5)	7 (13)		
Hospital, median (IQR), d	12.5 (9-19)	16 (11-24)	<0.0001	0.0002
<7 d, *n* (%)	20 (9)	3 (5)	0.03	0.08
7 to <14 d	103 (48)	22 (40)		
14 to <28 d	66 (31)	19 (35)		
≥28 d	27 (13)	11 (20)		
Opioids and/or benzodiazepines at hospital discharge, *n* (%)	58 (27)	14 (25)	0.85	0.74

HRQL=health-related quality of life. ITQOL=Infant and Toddler Quality of Life Questionnaire, from patients <2 years old or 2-6 years old with substantial developmental impairment. PRISM III-12=Pediatric Risk of Mortality III score from first 12 hours in the PICU. IQR=interquartile range. PARDS=pediatric acute respiratory distress syndrome. OI=oxygenation index. OSI=oxygen saturation index. NMB=neuromuscular blocking agent. HFOV=high-frequency oscillatory ventilation. ECMO=extracorporeal membrane oxygenation. MODS=multiple organ dysfunction syndrome. SBS=State Behavioral Scale. PICU=pediatric intensive care unit.

* *P* values for comparison between groups were calculated using logistic regression accounting for PICU as a cluster variable using generalized estimating equations, unless otherwise specified.

† *P* values were calculated as above, adjusting for age group (<1 y, 1 to <6 y) and PRISM III-12 score.

‡ Median household income of zip code of residence in 2011.[E2]

§ Severity of illness was defined by the PRISM III-12 score. The scale for the PRISM III-12 score ranges from 0 to 74, with higher scores indicating a higher risk of death.[E3]

‖ Other acute primary diagnoses include laryngotracheobronchitis, pertussis, acute respiratory failure related to multiple blood transfusions, pneumothorax (nontrauma), pulmonary edema, and pulmonary hemorrhage. Other chronic primary diagnoses include acute respiratory failure after bone marrow transplantation, acute exacerbation lung disease (cystic fibrosis or bronchopulmonary dysplasia), and pulmonary hypertension (not primary).

¶ PARDS severity was defined using the 2015 Pediatric Acute Lung Injury Consensus Conference (PALICC) criteria.[E4]

** *P* values were calculated using Fisher's exact test due to zero counts.

†† MODS was defined as respiratory dysfunction plus one or more extrapulmonary organ dysfunctions, with concurrent MODS defined by onset on day 0/1 and new MODS by onset on day 2 or later.[E5]

‡‡ Synthetic primary opioid agent includes fentanyl, hydromorphone, and remifentanil.

§§ Different sedative classes include opioids, benzodiazepines, α2-adrenergic agonists, propofol, barbiturates, ketamine, and chloral hydrate.

‖‖ Inadequate pain management was defined as pain score >4 (or pain assumed present if receiving neuromuscular blockade) for 2 consecutive hours and inadequate sedation management as SBS score >0 (or agitation assumed present if receiving neuromuscular blockade) for 2 consecutive hours.

¶¶ Clinically significant iatrogenic withdrawal was defined as rescue therapy (an opioid or benzodiazepine bolus or an increase in opioid or benzodiazepine infusion) to manage an increase in withdrawal symptoms for patients weaning from ≥5 days of opioids.

Table E3. PedsQL scores at 6 months post-discharge according to functional status at baseline

Variable	Normal function* (n = 343)	Impaired function* (n = 101)	Healthy population sample[E6] (n = 9430)	*P* value normal vs population†	*P* value impaired vs population†
Age at PedsQL, *n* (%)					
2 to 4 y	145 (42)	41 (41)			
5 to 7 y	76 (22)	30 (30)			
8 to 12 y	60 (17)	17 (17)			
13 to 17 y	62 (18)	13 (13)			
PedsQL scores, mean (SD)‡					
Total score	81.7 (18.0)	64.2 (21.9)	82.7 (15.4)	0.19	<0.0001
Physical functioning	82.8 (22.7)	57.6 (32.7)	84.5 (19.5)	0.67	<0.0001§
Psychosocial health	81.1 (17.4)	68.2 (20.1)	81.7 (15.2)	0.22	<0.0001
Emotional functioning	77.6 (21.6)	75.1 (22.2)	81.3 (16.5)	0.0003	0.01
Social functioning	86.8 (18.2)	65.2 (25.0)	83.7 (19.4)	0.03	<0.0001
School functioning‖	76.3 (23.1)	59.6 (27.2)	78.8 (19.6)	0.21	<0.0001

PedsQL=Pediatric Quality of Life Inventory. SD=standard deviation.
* Normal functional status at baseline is defined as Pediatric Cerebral Performance Category (PCPC) = 1 and Pediatric Overall Performance Category (POPC) = 1, while impaired functional status is defined as POPC>1.
† *P* values comparing functional group mean scores with reference population means were calculated using linear regression accounting for pediatric intensive care unit as a cluster variable using generalized estimating equations.
‡ Higher scores indicate better health-related quality of life.
§ Due to a convergence problem when using an exchangeable correlation structure, a working independence correlation structure was used.
‖ For the normal function group, missing 57% of school functioning scores in the 2 to 4 y age group and 3% in children 5 y or older. For the impaired function group, missing 56% of school functioning scores in the 2 to 4 y age group and 5% in children 5 y or older. Of the 107 children missing school functioning scores whose parent/guardian provided interview data, 95 (89%) were not enrolled in school, preschool, or daycare.

Table E4. Factors present at admission and hospital course variables according to impaired HRQL based on PedsQL total score in patients with normal functional status at baseline

Variable	Not impaired HRQL (n = 279)	Impaired HRQL (n = 64)	*P* value unadj*	*P* value adj†
Factors present at hospital admission				
Sociodemographic factors and pre-existing health status				
Age at PedsQL, *n* (%)			0.0007	
2 to 4 y	133 (48)	12 (19)		
5 to 7 y	60 (22)	16 (25)		
8 to 12 y	41 (15)	19 (30)		
13 to 17 y	45 (16)	17 (27)		
Female, *n* (%)	138 (49)	27 (42)	0.34	
Non-Hispanic white, *n*/total (%)	158/277 (57)	28/64 (44)	0.06	
Parent education, *n* (%)			0.03	
Some high school	15 (7)	8 (20)		
High school graduate/G.E.D.	48 (24)	9 (22)		
Some college or technical school	74 (36)	10 (24)		
College graduate/postgraduate	67 (33)	14 (34)		
Unknown, *n*	75	23		
Median household income of zip code of residence, *n* (%)‡			0.04	
<$40,000	58 (21)	11 (17)		
$40,000-$79,999	157 (56)	46 (72)		
≥$80,000	64 (23)	7 (11)		
Any medical history, *n* (%)				
Prematurity (<36 wk postmenstrual age)	20 (7)	2 (3)	0.25	
Asthma (prescribed bronchodilators or steroids)	68 (24)	18 (28)	0.51	
Cancer (current or previous diagnosis)	14 (5)	13 (20)	<0.0001	
Features of the presentation of acute illness				
PRISM III-12 score, median (IQR)§	8 (4-13)	10 (5-15)	0.0004	
Risk of mortality based on PRISM III-12 score, median (IQR), %	3.8 (1.3-14.2)	6.1 (1.7-29.2)	<0.0001	
Primary diagnosis category, *n* (%)			0.64	
Bronchiolitis or asthma (or reactive airway disease)	76 (27)	18 (28)		
Pneumonia or aspiration pneumonia	133 (48)	25 (39)		
Acute respiratory failure related to sepsis	41 (15)	12 (19)		
Other acute diagnoses‖	21 (8)	7 (11)		
Other chronic diagnoses‖	8 (3)	2 (3)		
Hospital course variables				
Moderate/severe PARDS based on worst OI or OSI during hospitalization, *n* (%)¶	206 (74)	53 (83)	0.12	0.18
Early NMB (for the entire duration of days 1 and 2), *n* (%)	51 (18)	11 (17)	0.79	0.39
HFOV, *n* (%)	35 (13)	11 (17)	0.30	0.41
ECMO, *n* (%)	8 (3)	5 (8)	0.11	0.25
Non-invasive ventilation prior to intubation, *n* (%)	104 (37)	28 (44)	0.34	0.21
Non-invasive ventilation post-extubation, *n* (%)	106 (38)	24 (38)	0.94	0.86
Duration of mechanical ventilation, median (IQR), d	5.0 (3.1-8.7)	6.8 (4.0-12.3)	0.01	0.01**
<7 d, *n* (%)	184 (66)	34 (53)	0.14	0.09**
7 to <14 d	66 (24)	17 (27)		
14 to <28 d	22 (8)	7 (11)		
≥28 d (including transfers by day 28)	7 (3)	6 (9)		
MODS (concurrent or new), *n* (%)††	216 (77)	59 (92)	0.03	0.09
Extrapulmonary organ dysfunction during hospitalization, *n* (%)				
Cardiovascular	151 (54)	38 (59)	0.45	0.47
Neurologic	142 (51)	35 (55)	0.69	0.84
Hematologic	56 (20)	21 (33)	0.01	0.27
Renal	19 (7)	9 (14)	0.09	0.22
Hepatic	66 (24)	26 (41)	0.02	0.16
Number of organ dysfunctions, median (IQR)	2 (2-3)	3 (2-4)	0.01	0.28
Mean daily opioid dose, median (IQR), mg/kg	1.6 (1.0-2.8)	2.0 (1.0-3.6)	0.13	0.03
Mean daily benzodiazepine dose, median (IQR), mg/kg	1.5 (0.9-2.6)	1.8 (0.8-3.3)	0.15	0.02
Synthetic primary opioid agent, *n* (%)‡‡	195 (70)	43 (67)	0.58	0.41
Dexmedetomidine, *n* (%)	119 (43)	31 (48)	0.33	0.28
Clonidine, *n* (%)	33 (12)	14 (22)	0.09	0.03
Ketamine, *n* (%)	106 (38)	21 (33)	0.48	0.51

Barbiturates, *n* (%)	46 (16)	11 (17)	0.90	0.48
Methadone, *n* (%)	60 (22)	15 (23)	0.69	0.93
Antidelirium medication, *n* (%)	8 (3)	4 (6)	0.19	0.86
≥4 sedative classes, *n* (%)§§	97 (35)	24 (38)	0.66	0.57
Study days awake and calm (daily modal SBS score -1 or 0), median (IQR), %	79 (60-100)	71 (44-93)	0.14	0.09
Heavy sedation (daily modal SBS score ever -3), *n* (%)	35 (13)	16 (25)	0.003	0.06
Inadequate pain management, *n* (%)‖	35 (13)	16 (25)	0.002	0.003
Inadequate sedation management, *n* (%)‖	50 (18)	20 (31)	0.009	0.003
Clinically significant iatrogenic withdrawal, *n* (%)¶	33 (12)	6 (9)	0.53	0.94
Length of stay				
PICU, median (IQR), d	8.2 (5.1-13.1)	10.9 (6.4-17.6)	0.02	0.03
<7 d, *n* (%)	111 (40)	18 (28)	0.09	0.07
7 to <14 d	104 (37)	24 (38)		
14 to <28 d	52 (19)	13 (20)		
≥28 d	12 (4)	9 (14)		
Hospital, median (IQR), d	13 (8-22)	19 (11-32)	0.003	0.02
<7 d, *n* (%)	44 (16)	3 (5)	0.02	0.06
7 to <14 d	111 (40)	21 (33)		
14 to <28 d	79 (28)	18 (28)		
≥28 d	45 (16)	22 (34)		
Opioids and/or benzodiazepines at hospital discharge, *n* (%)	78 (28)	26 (41)	0.03	0.04

HRQL=health-related quality of life. PedsQL=Pediatric Quality of Life Inventory. PRISM III-12=Pediatric Risk of Mortality III score from first 12 hours in the PICU. IQR=interquartile range. PARDS=pediatric acute respiratory distress syndrome. OI=oxygenation index. OSI=oxygen saturation index. NMB=neuromuscular blocking agent. HFOV=high-frequency oscillatory ventilation. ECMO=extracorporeal membrane oxygenation. MODS=multiple organ dysfunction syndrome. SBS=State Behavioral Scale. PICU=pediatric intensive care unit.

* *P* values for comparison between groups were calculated using logistic regression accounting for PICU as a cluster variable using generalized estimating equations.

† *P* values were calculated as above, adjusting for age group and PRISM III-12 score.

‡ Median household income of zip code of residence in 2011.[E2]

§ Severity of illness was defined by the PRISM III-12 score. The scale for the PRISM III-12 score ranges from 0 to 74, with higher scores indicating a higher risk of death.[E3]

‖ Other acute primary diagnoses include pulmonary edema, thoracic trauma, pulmonary hemorrhage, laryngotracheobronchitis, and pulmonary embolus. Other chronic primary diagnoses include acute chest syndrome/sickle cell disease, acute respiratory failure after bone marrow transplantation, and acute exacerbation lung disease (cystic fibrosis or bronchopulmonary dysplasia).

¶ PARDS severity was defined using the 2015 Pediatric Acute Lung Injury Consensus Conference (PALICC) criteria.[E4]

** Due to a convergence problem when using an exchangeable correlation structure, a working independence correlation structure was used.

†† MODS was defined as respiratory dysfunction plus one or more extrapulmonary organ dysfunctions, with concurrent MODS defined by onset on day 0/1 and new MODS by onset on day 2 or later.[E5]

‡‡ Synthetic primary opioid agent includes fentanyl, hydromorphone, and remifentanil.

§§ Different sedative classes include opioids, benzodiazepines, α2-adrenergic agonists, propofol, barbiturates, ketamine, and chloral hydrate.

‖‖ Inadequate pain management was defined as pain score >4 (or pain assumed present if receiving neuromuscular blockade) for 2 consecutive hours and inadequate sedation management as SBS score >0 (or agitation assumed present if receiving neuromuscular blockade) for 2 consecutive hours.

¶¶ Clinically significant iatrogenic withdrawal was defined as rescue therapy (an opioid or benzodiazepine bolus or an increase in opioid or benzodiazepine infusion) to manage an increase in withdrawal symptoms for patients weaning from ≥5 days of opioids.

References

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