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The Modified Clinical Progression Scale for Pediatric Patients: Evaluation as a Severity Metric and Outcome Measure in Severe Acute Viral Respiratory Illness.

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OPEN

The Modified Clinical Progression Scale for Pediatric Patients: Evaluation as a Severity Metric and Outcome Measure in Severe Acute Viral Respiratory Illness

OBJECTIVES: To develop, evaluate, and explore the use of a pediatric ordinal score as a potential clinical trial outcome metric in children hospitalized with acute hypoxic respiratory failure caused by viral respiratory infections.

DESIGN: We modified the World Health Organization Clinical Progression Scale for pediatric patients (CPS-Ped) and assigned CPS-Ped at admission, days 2–4, 7, and 14. We identified predictors of clinical improvement (day 14 CPS-Ped ≤ 2 or a three-point decrease) using competing risks regression and compared clinical improvement to hospital length of stay (LOS) and ventilator-free days. We estimated sample sizes (80% power) to detect a 15% clinical improvement.

SETTING: North American pediatric hospitals.

PATIENTS: Three cohorts of pediatric patients with acute hypoxic respiratory failure receiving intensive care: two influenza (pediatric intensive care influenza [PICFLU], $n = 263$, 31 sites; PICFLU vaccine effectiveness [PICFLU-VE], $n = 143$, 17 sites) and one COVID-19 ($n = 237$, 47 sites).

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Invasive mechanical ventilation rates were 71.4%, 32.9%, and 37.1% for PICFLU, PICFLU-VE, and COVID-19 with less than 5% mortality for all three cohorts. Maximum CPS-Ped (0 = home at respiratory baseline to 8 = death) was positively associated with hospital LOS ($p < 0.001$, all cohorts). Across the three cohorts, many patients' CPS-Ped worsened after admission (39%, 18%, and 49%), with some patients progressing to invasive mechanical ventilation or death (19%, 11%, and 17%). Despite this, greater than 76% of patients across cohorts clinically improved by day 14. Estimated sample sizes per group using CPS-Ped to detect a percentage increase in clinical improvement were feasible (influenza 15%, $n = 142$; 10%, $n = 225$; COVID-19, 15% $n = 208$) compared with mortality ($n > 21{,}000$, all), and ventilator-free days (influenza 15%, $n = 167$).

CONCLUSIONS: The CPS-Ped can be used to describe the time course of illness and threshold for clinical improvement in hospitalized children and adolescents with acute respiratory failure from viral infections. This outcome measure could feasibly be used in clinical trials to evaluate in-hospital recovery.

KEY WORDS: acute hypoxic respiratory failure; acute respiratory distress syndrome; children; critical care; respiratory outcome score

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Severe acute respiratory infections in children can progress to acute respiratory failure and life-threatening acute respiratory distress syndrome (ARDS), with high associated morbidity and mortality (1–6). The prevalence of ARDS in the pediatric population, and its associated mortality, is lower

RESEARCH IN CONTEXT

- Severe acute respiratory infections in pediatric patients can progress to respiratory failure and acute respiratory distress syndrome (ARDS). Conducting clinical trials on pediatric ARDS is challenging because mortality is uncommon, and the use of noninvasive ventilation strategies is frequent.
- Ordinal scoring systems incorporate a range of clinically relevant outcomes into a single composite endpoint to improve the efficiency of trial design.
- Our aim was to modify the World Health Organization Clinical Progression Scale (WHO-CPS) for pediatric patients, to evaluate this score using real-world data, and to estimate how the use of this score might influence sample size and statistical power.

in children compared with adults (7). The use of invasive arterial oxygen monitoring is, therefore, less frequent, and management with noninvasive ventilation is more common than in adults with ARDS (8, 9).

The Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) guidelines for the diagnosis and management of pediatric ARDS (PARDS) were published in 2023 (10). Key differences in the PALICC-2 PARDS definition compared to the adult ARDS Berlin definition (11) includes the use of pulse oximetry if arterial blood oxygenation measurements are not available, the use of the oxygenation index and oxygenation saturation index (OSI) to assess hypoxemia and presence of new infiltrates consistent with acute pulmonary parenchymal disease as opposed to bilateral infiltrates. Conducting PARDS clinical trials is challenging because mortality or days alive and free of mechanical ventilation (ventilator-free days or VFD) require many patients to detect a clinically meaningful effect (12, 13), and patients who do not yet require mechanical ventilation but are at risk for developing acute respiratory failure are excluded.

Ordinal scores have been used for trial outcomes in adults with ARDS (14, 15), severe influenza (16, 17), and COVID-19 (18–23). These scores allow the inclusion of patients on a range of support, including noninvasive ventilation and high-flow nasal cannula, both commonly used in children (24). Such a score may facilitate the prospective enrollment of children into randomized trials, especially during pandemics (25). Our aim was to develop an ordinal respiratory outcome score for pediatric patients to capture the spectrum of illness severity, to evaluate this score using real-world data from PICU patients requiring respiratory support for severe acute viral LRTIs, and to estimate how the use of this score might influence statistical power.

METHODS

We analyzed data from three prospectively enrolled pediatric multicenter North American cohorts admitted to the PICU or high acuity unit. The pediatric intensive care influenza (PICFLU) study (26) and PICFLU vaccine effectiveness (PICFLU-VE) study (27) included children admitted with confirmed influenza infection (n = 263 admitted 2009–2018 across 31 sites; n = 143 admitted 2019–2020 across 17 sites, respectively). The Overcoming COVID-19 Public Health Surveillance Registry included 237 prospectively enrolled children and adolescents across 47 sites with acute COVID-19 requiring pediatric intensive care from March 2020 to December 2020 (28, 29). Study approval was obtained from the Boston Children's Hospital institutional review board (IRB) (PICFLU: X08-11-0534, PICFLU-VE: IRB-P00033157, COVID: IRB-P00009548; additional details in **online data supplement**, http://links.lww.com/PCC/C409). Informed consent was obtained for PICFLU and PICFLU-VE; informed consent was waived for COVID-19. Enrollment criteria and variable definitions have been published (26–29) and are available along with outcome definitions in the online data supplement (http://links.lww.com/PCC/C409). We excluded patients on chronic ventilatory support because we did not have information on home settings to assess return to baseline. We also excluded patients who received no continuous oxygen by hospital day 4, as receipt of minimal respiratory support would likely trigger eligibility for trial enrollment.

Development of the Clinical Progression Scale for Pediatrics (CPS-Ped)

We modified the World Health Organization (WHO) Clinical Progression Scale (CPS) (19) to create a

Clinical Progression Scale for Pediatrics (CPS-Ped) including PARDS severity classifications based on PALICC-2 criteria (10). The WHO-CPS was developed in 2020 by an international panel of experts who met in Geneva, Switzerland. Using a Delphi process, participants agreed on an ordinal scale measuring patient progression through the healthcare system and reflecting trajectory and resource use over the clinical course. The CPS-Ped stratifies patients based on the amount of respiratory support (low-flow or high-flow nasal cannula oxygen, noninvasive or invasive mechanical ventilation), including different scores for patients discharged home at respiratory baseline versus requiring additional respiratory support, similar to Beigel et al (16, 18). A detailed comparison of CPS-Ped to the WHO-CPS is shown in **Table 1** and a comparison of CPS-Ped, WHO-CPS, and two other adult scores is shown in **Table e1** (http://links.lww.com/PCC/C409).

The CPS-Ped depicts a nine-point ordinal progression from 0 to 8. Patients with PARDS are scored 6–7 and death is scored 8. Unlike the WHO-CPS, the CPS-Ped does not include viral testing, because asymptomatic viral testing is not common practice. Dialysis use was not included in CPS-Ped because it was rare. Vasopressor requirements were not included in the score, but we did assess how the addition of vasopressors would change the score and outcome in post hoc analyses.

Evaluation of the Clinical Progression Score for Pediatrics (CPS-Ped)

We evaluated the performance of the CPS-Ped in three cohorts of pediatric patients admitted to the PICU. CPS-Ped was used to describe the escalation and de-escalation of respiratory support and capture which patients met the criteria for clinical improvement.

TABLE 1.
Comparison of World Health Organization Clinical Progression Scale and Clinical Progression Scale—Pediatrics

Clinical Status	World Health Organization Clinical Progression Scale (19)	Clinical Progression Scale–Pediatrics
Uninfected or recovered	0: Uninfected, no viral RNA detected	0: At respiratory baseline
Ambulatory; mild disease	1: Asymptomatic, viral RNA detected 2: Symptomatic, independent 3: Symptomatic, assistance needed	1: At home on new respiratory support[a] or in rehabilitation
Hospitalized; moderate disease	4: No oxygen therapy 5: Receiving oxygen by mask or nasal prongs	2: No oxygen therapy 3: Receiving oxygen by mask or nasal prongs
Hospitalized; severe disease	6: HFNC or NIPPV 7: IMV; $Pao_2/Fio_2 \geq 150$ ($Spo_2/Fio_2 \geq 200$) 8: IMV; $Pao_2/Fio_2 < 150$ ($Spo_2/Fio_2 < 200$) or vasopressors 9: IMV; $Pao_2/Fio_2 < 150$ and vasopressors, dialysis, or ECMO	4: HFNC or NIPPV 5: IMV without ARDS (OI ≤ 4 or OSI ≤ 5)[b] 6: IMV with mild/moderate ARDS ($4 < OI < 16$ or $5 < OSI < 12$)[a] 7: IMV with severe ARDS (OI ≥ 16 or OSI ≥ 12)[a] or ECMO
Death	10: Death	8: Death

ECMO = extracorporeal membrane oxygenation, HFNC = high-flow nasal cannula, IMV = invasive mechanical ventilation, NIPPV = noninvasive positive pressure ventilation, OI = oxygenation index, OSI = oxygenation saturation index, PARDS = pediatric acute respiratory distress syndrome, Spo_2 = peripheral oxygen saturation.

[a]New respiratory support includes patients who are discharged from the hospital on new (or increased) supplementary oxygen, new NIPPV, or new ventilator dependence.

[b]PARDS definitions based on Second Pediatric Acute Lung Injury Consensus Conference (10).

Formulas: $OI = (Fio_2 \times \text{mean airway pressure} \times 100)/Pao_2$; $OSI = (Fio_2 \times \text{mean airway pressure} \times 100)/Spo_2$.

Patients were assigned a CPS-Ped score on admission and days 2–4, 7, 14, and 28. For each cohort, clinical improvement was defined on day 14 as CPS-Ped of two or less or a decrease of at least three points from admission. A score of two or less indicates that a patient no longer requires acute respiratory support in the hospital or has been discharged home. Patients still requiring respiratory support, but whose score decreased at least three points, were alive and liberated from invasive mechanical ventilation, similar to VFD. Because almost all survivors had recovered by day 28, we chose day 14 as our endpoint.

We compared clinical improvement based on the CPS-Ped to VFD at day 14 (13), hospital length of stay (LOS), and mortality. We performed sample size and power calculations to determine the sample size required per group for detecting a 15% relative difference in day 14 clinical improvement, VFD, and mortality. Post hoc analyses to determine if differences in Spo_2 measurements in Black patients would change criteria for clinical improvement at day 14, and to estimate the effect of incorporating vasopressors into the score were conducted.

Statistical Analyses

Continuous and categorical data were summarized as medians (interquartile range), and all categorical data are presented as frequencies (percentages). Univariate and multivariable analyses of predictors of recovery at day 14 were assessed to identify patient characteristics that should be balanced in the randomization of future clinical trials. This analysis was performed using the Fine-Gray regression model, with mortality before day 14 as a competing event to account for informative censoring (30). Results are reported as adjusted hazard ratios with 95% CIs. A two-tailed p value of less than 0.05 was considered statistically significant. For 80% and 90% power, the sample size required per group for detecting a 15% relative difference (alpha 5% two-tailed) in day 14 clinical improvement, VFD, and mortality were calculated. Additional details of the statistical analyses, including sample size and power calculations for a 10% and 20% relative difference, are in the online data supplement (http://links.lww.com/PCC/C409).

RESULTS

As shown in **Table 2**, the three pediatric cohorts had similarities and differences. Patients in PICFLU and PICFLU-VE were younger than in COVID-19 (6.2 and 4.9 yr vs 13.6 yr, respectively). The PICFLU cohort also had a higher percentage of previously healthy patients (65.4%) and bacterial coinfection (35.4%) compared with PICFLU-VE (23.1%, 14.7%) and COVID-19 (21.9%, 6.3%). Importantly, the PICFLU cohort had a higher frequency of life-threatening disease with higher rates of invasive mechanical ventilation (71.5%) and extracorporeal membrane oxygenation (ECMO) support (12.9%) compared with PICFLU-VE (32.9%, 2.1%) and COVID-19 (37.1%, 3.8%). In-hospital mortality was 4.9% in PICFLU, 2.1% in PICFLU-VE, and 4.6% in COVID-19.

Assessment of Disease Severity Using CPS-Ped and Associations With Other Outcomes

The majority of patients in each cohort met clinical improvement criteria by day 14, including 205 of 263 patients (77.9%) of PICFLU, 125 of 143 patients (87.4%) of PICFLU-VE, and 182 of 237 patients (76.8%) of COVID-19 patients. In the PICFLU cohort, 36% of patients met criteria for PARDS (CPS-Ped 6 or 7) (10) on admission, which was higher than in the other two cohorts (**Fig. 1*A***). In the COVID-19 cohort, despite lower rates of mechanical ventilation than in PICFLU, the distribution of CPS-Ped over time shows a higher proportion of patients with persistent need for respiratory support (CPS-Ped score of ≥ 3) at days 7 and 14 (Fig. 1*A*). Among survivors in all three cohorts, hospital LOS was longest in patients that developed PARDS (CPS-Ped 6 or 7) (10) (**Fig. 1*B***); there was a positive association between maximum CPS-Ped from admission to day 14 and hospital LOS in survivors ($p < 0.001$), a commonly used measure for recovery. There was also a significant correlation between patients who met criteria for clinical improvement at day 14 and VFD between all three cohorts ($p < 0.001$), despite the lower frequency of invasive mechanical ventilation in PICFLU-VE and COVID-19 (**Fig. e1**, http://links.lww.com/PCC/C409).

Although Figure 1*A* shows that there is overall improvement in CPS-Ped scores in survivors over time, many patients had increased disease severity on hospital day 2 or later. Combining patients from all three cohorts, **Figure 2*A*** shows an alluvial plot of CPS-Ped progression through day 14 color-coded by day 14 CPS-Ped. The percentage of patients experiencing

TABLE 2.
Patient Demographics and Clinical Characteristics of the Pediatric Intensive Care Influenza Cohorts and the COVID-19 Cohort

Variable	PICFLU (*n* = 263)	PICFLU-VE (*n* = 143)	COVID-19 (*n* = 237)
Age (yr), median (IQR)	6.2 (2.1, 10.9)	4.9 (2.4, 9.0)	13.6 (4.6, 16.4)
Sex, *n* (%)			
Male	152 (57.8)	91 (63.6)	146 (61.6)
Female	111 (42.2)	52 (36.4)	91 (38.4)
Race, *n* (%)			
White	192 (73.0)	87 (60.8)	106 (44.7)
Black	42 (16.0)	22 (15.4)	74 (31.2)
Asian	4 (1.5)	5 (3.5)	10 (4.2)
Multirace or other	25 (9.5)	29 (20.3)	47 (19.8)
Ethnicity, *n* (%)			
Hispanic or Latino	62 (23.6)	33 (23.1)	84 (35.4)
Not Hispanic or Latino or unknown	201 (76.4)	110 (76.9)	153 (64.6)
Underlying health issues, *n* (%)			
Previously healthy	172 (65.4)	50 (35.0)	52 (21.9)
Respiratory	64 (24.3)	57 (39.9)	91 (38.4)
Asthma	51 (19.4)	37 (25.9)	58 (24.5)
Cardiovascular	2 (0.8)	7 (4.9)	35 (14.8)
Neurologic	23 (8.7)	40 (28.0)	53 (22.4)
Other[a]	28 (10.6)	54 (37.8)	159 (67.1)
Influenza type, *n* (%)[b]			
Influenza A	198 (75.3)	89 (62.2)	
Influenza B	59 (22.4)	51 (35.7)	
Bacterial coinfection, *n* (%)	93 (35.4)	21 (14.7)	15 (6.3)
Viral codetection, *n* (%)	56 (21.3)	28 (19.6)	20 (8.4)
Vasoactive infusions[c], *n* (%)	91 (34.6)	31 (21.7)	41 (17.3)
Mechanical ventilation, *n* (%)	188 (71.5)	47 (32.9)	88 (37.1)
Extracorporeal membrane oxygenation, *n* (%)	34 (12.9)	3 (2.1)	9 (3.8)
Invasive mechanical ventilation days[d], median (IQR)	3.3 (0.0, 7.3)	0 (0, 1.6)	0 (0, 3.3)
PICU days, median (IQR)	6.0 (3.2, 11.8)	2.5 (1.5, 6.2)	4.8 (2.4, 10.4)
Hospital days[e], median (IQR)	9.5 (5.0, 19.2)	5.7 (3.4, 12.2)	9.0 (4.8, 16.1)
Hospital mortality, *n* (%)	13 (4.9)	3 (2.1)	11 (4.6)

IQR = interquartile range, PICFLU = pediatric intensive care influenza, VE = vaccine effectiveness.

[a]Renal, gastrointestinal, hepatic, metabolic, and genetic conditions.

[b]Influenza A H1N1 subtype was identified in 96 (36.5%) PICFLU patients and 75 (52.4%) PICFLU-VE patients. Influenza A H3 subtype was identified in 61 (23.2%) PICFLU patients and 2 (1.4%) PICFLU-VE patients. Influenza A (not subtyped) was identified in 41 (15.6%) PICFLU patients and 12 (8.4%) PICFLU-VE patients.

[c]Patients who received vasoactive infusions (dopamine > 5 μg/kg/min or any dose of epinephrine/norepinephrine) on any day during hospitalization.

[d]Among survivors; does not include noninvasive positive pressure ventilation days.

[e]Referring hospital hours if known.

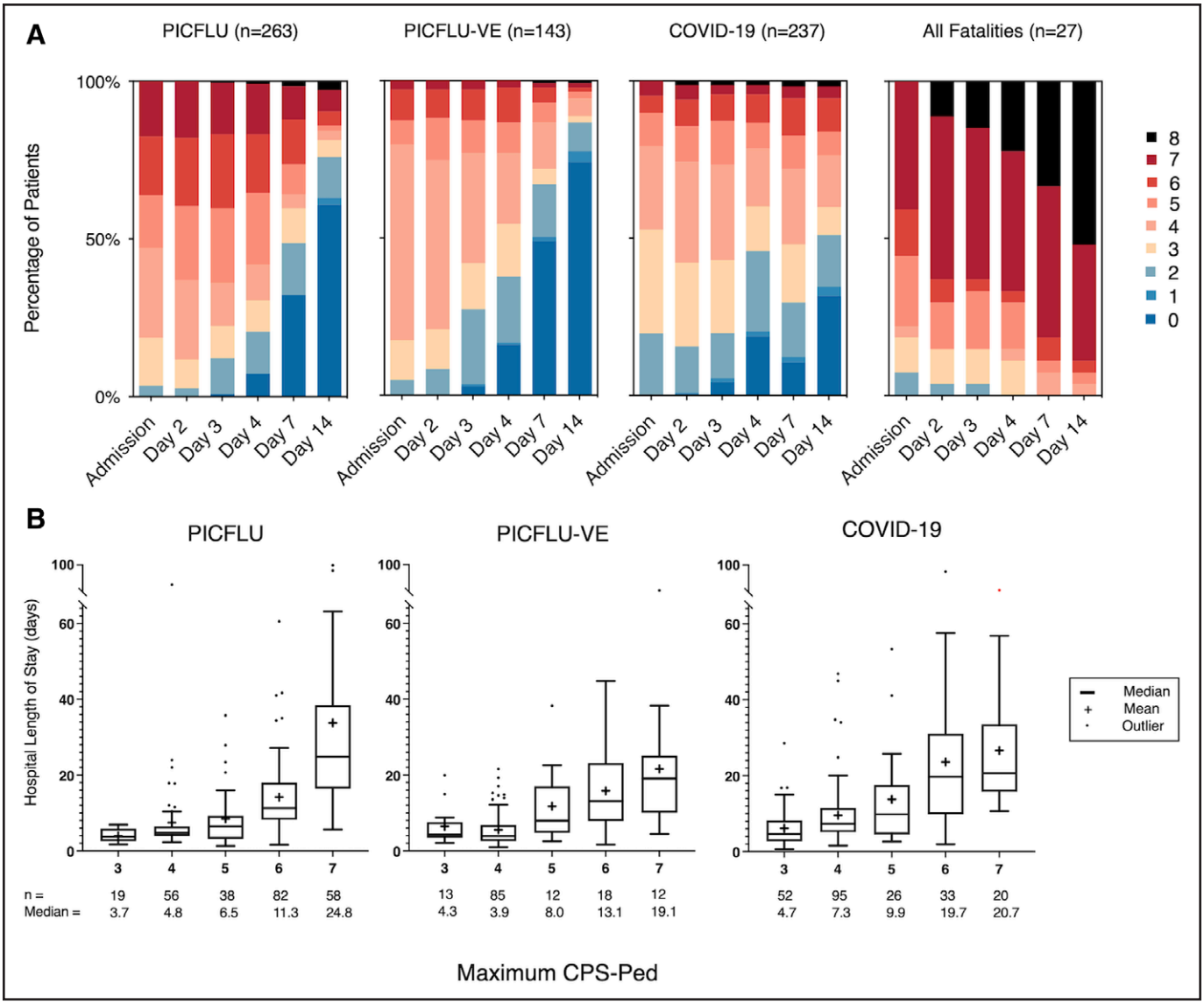

Figure 1. The Clinical Progression Scale—Pediatric (CPS-Ped) distribution. **A**, Distribution of the CPS-Ped by hospital day through day 14 for the Pediatric Intensive Care Influenza (PICFLU), PICFLU-vaccine effectiveness (VE), and COVID-19 cohorts, and for fatalities across all three cohorts ($n = 27$; PICFLU = 13; PICFLU-VE = 3; COVID-19 = 11). None of the patients who died (CPS-Ped 8) met the criteria for clinical improvement during their hospitalization. **B**, Association of maximum CPS-Ped by day 14 in survivors versus total hospital length of stay using the Kruskal-Wallis test.

clinical worsening (CPS-Ped increasing ≥ 1 point) at any point from admission to day 14 was 39.1% in PICFLU, 18.2% in PICFLU-VE, and 48.9% in COVID-19; in these same cohorts, 19.0%, 11.2%, and 16.9% of patients progressed to require intubation and/or death by day 14. Additional details of the trajectory of change in CPS-Ped after admission through hospital day 14 are in **Table e2** (http://links.lww.com/PCC/C409).

Of the 27 in-hospital deaths, deaths occurring on or before day 14 were uncommon (n = 14; 7 PICFLU, 1 PICFLU-VE, 6 COVID-19). An alluvial plot showing the progression of CPS-Ped for all in-hospital fatalities is shown in **Figure 2*B***. An analysis of CPS-Ped progression for fatalities that occurred at any point during hospitalization showed that none of the patients who died met criteria for clinical improvement by day 14 or during their hospitalization, although some were still alive by day 28.

Factors Associated With Clinical Improvement by Day 14

Details of the results of the univariate and multivariate analyses are in **Table e3** (http://links.lww.com/PCC/C409). Higher admission CPS-Ped was associated

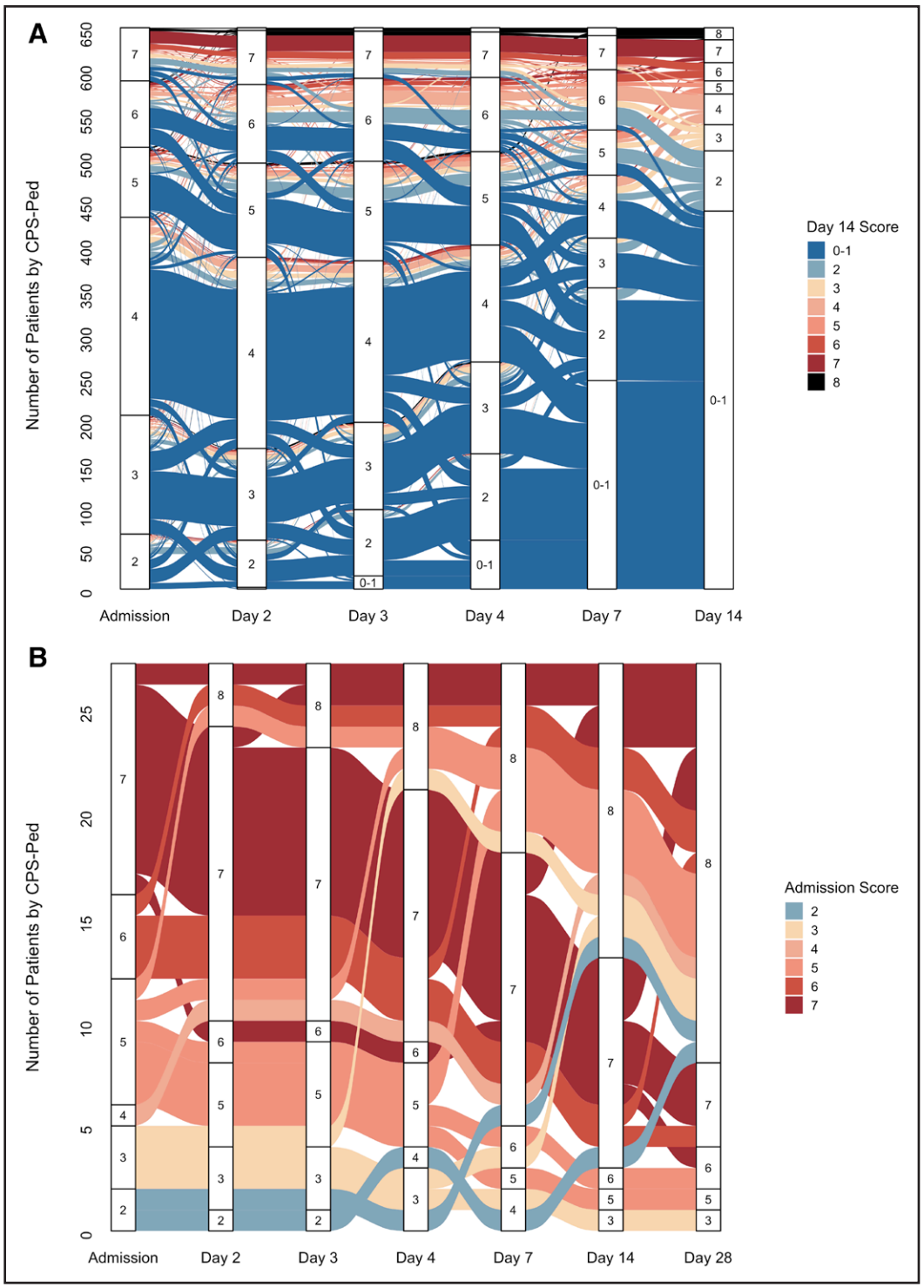

Figure 2. Alluvial plots of the Clinical Progression Scale—Pediatric (CPS-Ped). **A**, Alluvial plot of the CPS-Ped through day 14 for all three cohorts. Patients are color-coded by CPS-Ped on day 14. The legend shows the color-coding of CPS-Ped from 0 (discharged home at baseline support) through 8 (death). **B**, Alluvial plot of the CPS-Ped for fatalities for all three cohorts. Patients are color-coded by CPS-Ped on admission. The legend shows the color-coding of CPS-Ped from 2 (in hospital, no respiratory support) through 8 (death).

with failure to clinically improve by day 14 in all three cohorts ($p \leq 0.05$) in univariate analyses. Other significant predictors of a lower likelihood of clinical improvement by day 14 included age of greater than 12 years in PICFLU, and bacterial coinfection in PICFLU and PICFLU-VE. The results of the multivariable analyses adjusted for age category, gender, race, ethnicity, and bacterial coinfection are in **Figure 3**; after adjustment, admission CPS-Ped remained significant only in the PICFLU cohort.

Sample Size Calculations

Detailed sample size estimates for detecting a 10%, 15%, or 20% clinical improvement using CPS-Ped, VFD, and mortality are shown in **Table e4** (http://links.lww.com/PCC/C409) using the observed outcome percentages for each cohort as control group estimates. When using CPS-Ped to assess clinical improvement by day 14, the sample size estimated to detect a 15% relative difference in clinical improvement

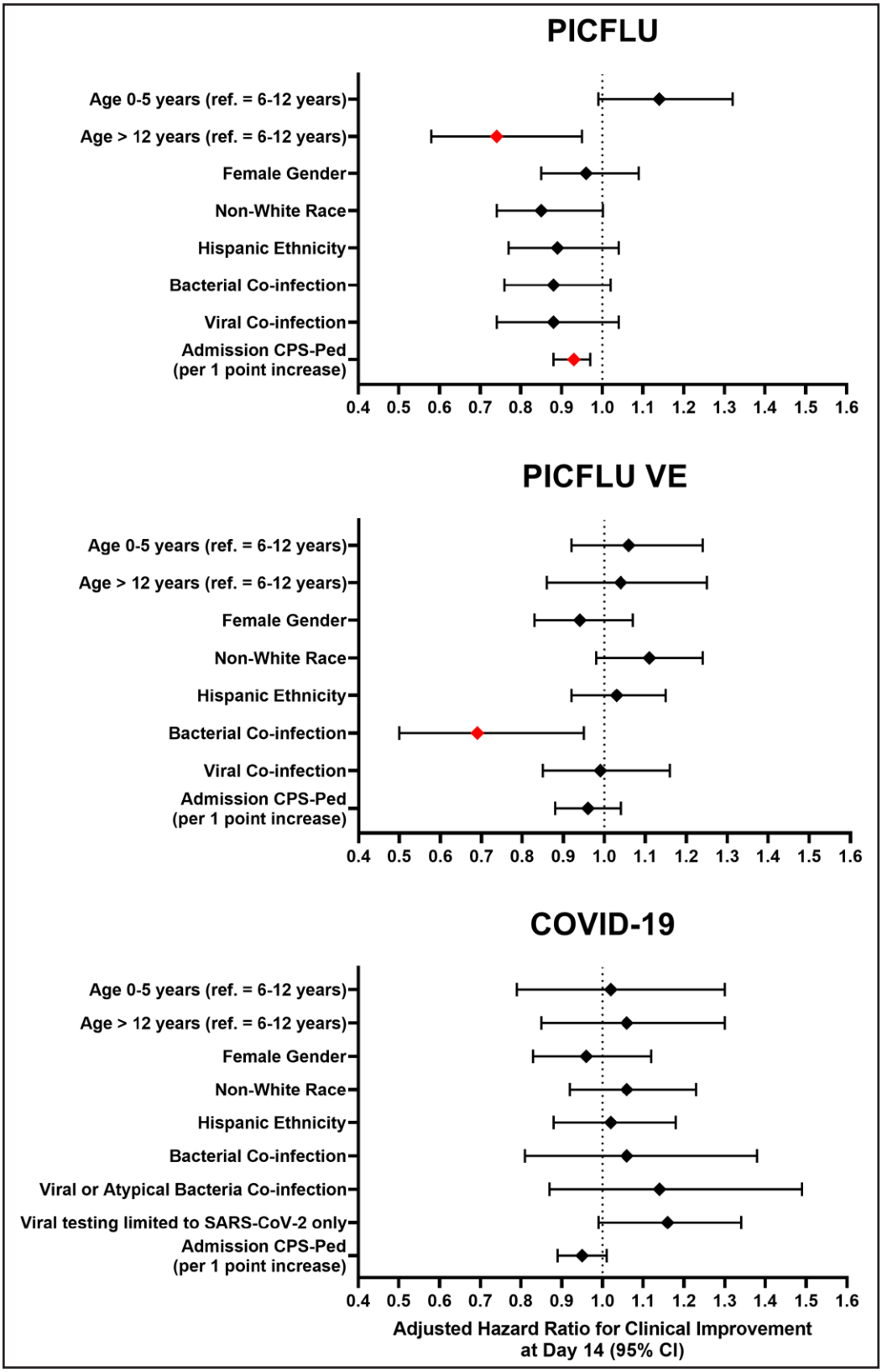

Figure 3. Predictors of clinical improvement using the Clinical Progression Scale—Pediatric (CPS-Ped) at day 14 in the Pediatric Intensive Care Influenza (PICFLU), PICFLU-vaccine effectiveness (VE), and pediatric COVID-19 cohorts. Clinical improvement was defined as a CPS-Ped of ≤ 2 or a decrease from the maximum CPS-Ped by three points at day 14. Associations were evaluated in the multivariable analyses using the Fine-Gray regression model with early mortality as a competing event. SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

in the intervention group compared to the control group for PICFLU and COVID-19 with 80% power was 142 and 208, respectively, per group. For PICFLU-VE, a 15% improvement would require that 98% of patients clinically improved by day 14, given that the control group already had 85% clinical improvement by that date. To detect a 10% clinical improvement with 80% power in PICFLU-VE, 225 patients per group would be required.

We then calculated sample size estimates for other relevant clinical outcomes. For VFDs, detecting a 15% relative improvement in VFDs at day 14 required 167 patients per treatment group for PICFLU. For the PICFLU-VE and COVID-19 cohorts, it was not possible to perform these calculations because the median VFD at day 14 was 14, therefore not allowing the detection of a response effect within the intervention group. For mortality, the sample size estimates per treatment group to provide 80% power with 15% relative improvement in a population with a 3% baseline mortality rate (which is

AT THE BEDSIDE

- Clinical Progression Scale—Pediatrics (CPS-Ped) captures a wide range of disease severity based on the level of respiratory support and degree of hypoxia in pediatric patients with acute viral respiratory infections.
- In contrast to ventilator-free days, CPS-Ped captured clinical improvement in nonintubated patients and allowed for tracking of disease severity over time.
- Clinical improvement by day 14 using CPS-Ped was correlated with hospital length of stay and sample sizes appear feasible as a potential outcome measure to evaluate in-hospital recovery for future clinical trials.

consistent with what was observed in the PICFLU cohort), was 21,356 patients per treatment group; for the other two cohorts with lower mortality sample size estimates were even larger.

Post hoc Analyses

Our first post hoc analysis was to determine whether potential decreases in Spo_2 compared to Pao_2 measurements in Black patients would impact clinical improvement by day 14. Among the three cohorts, 30 Black patients had a total of 86 OSI measurements at any point during their hospitalization; only three scores would change if Spo_2 were decreased by 4% (details in online data supplement, http://links.lww.com/PCC/C409). Our second post hoc analysis evaluated how adding vasopressors to CPS-Ped would change clinical improvement by day 14. Of patients with a maximum CPS-Ped score of less than 7, the number of patients who met the criteria for clinical improvement by day 14 increased by 11 patients; their maximum score increased from 6 to 7 and their day 14 score was 4, so the change of three points led to them meet clinical improvement criteria (**Table e5**, http://links.lww.com/PCC/C409).

DISCUSSION

We developed CPS-Ped as an ordinal score describing the range of disease severity based on the level of respiratory support and degree of hypoxia in pediatric patients requiring intensive care for viral lower respiratory tract infection (LRTI). We compared CPS-Ped against another indicator of recovery, hospital LOS in survivors. Our findings suggest that in future randomized clinical trials including children with viral LRTI, it is important to ensure age, infecting virus type, bacterial coinfection, and admission disease severity are balanced across the groups as each predicts clinical improvement.

Use of noninvasive ventilatory strategies in children with acute viral respiratory failure is increasingly common and often avoids the need for invasive mechanical ventilation. Thus, CPS-Ped showed superiority over VFD as a clinical outcome as CPS-Ped captures improvement in nonintubated patients. CPS-Ped also allowed tracking of disease severity over time and identified patients who developed PARDS. Mortality was low in all three cohorts and would require many thousands of patients per group to detect a difference, making it infeasible as an outcome.

We did not identify a score similar to CPS-Ped for children, but ordinal scores have been used as clinical trial endpoints for adult viral LRTI. In 2019, Beigel et al (16) used clinical status at day 7 on a six-point ordinal scale in a randomized trial of anti-influenza plasma for severe influenza A infection. The WHO-CPS was developed for COVID-19 trials (19), and a trial of remdesivir in adults hospitalized with COVID-19 used an eight-category ordinal scale to define clinical improvement at day 15 (18). CPS-Ped, a similarly constructed ordinal outcome assessment score, could be applied in pediatric trials. Potential advantages of using this composite endpoint include increased statistical power and holistic assessment of treatment effectiveness, which may lead to improved clinical relevance and efficiency of trial design.

There are several considerations that should be mentioned regarding the use of CPS-Ped as an ordinal score. Scores of 0, 1, and 8 are outcome measures and, by definition, cannot be present at admission. Scores 3 and 4 are potentially influenced by practitioner behavior, local practice, and patient characteristics due to variability on when to initiate and escalate oxygen therapy and noninvasive support. In contrast, scores of 5, 6, and 7 represent a more objective use of invasive mechanical ventilation and/or ECMO. Clinicians should also be mindful of recently published literature describing differences between simultaneous Sao_2 and Spo_2 measurements in Black patients compared to

White patients (31, 32), showing possible underestimation of hypoxia in dark-skinned patients when pulse oximetry measurements are used. This is important to consider as the use of OSI in the CPS-Ped could lead to misclassification, although our post hoc analysis of OSI measurements in Black patients did not suggest significant bias was introduced in these three cohorts.

Short-term in-hospital outcomes are feasibly measured, but their associations with longer-term health outcomes are unclear. However, we do believe that clinical improvement measured by CPS-Ped is likely to be clinically important. The First Line Support for Assistance in Breathing in Children (FIRST-ABC) clinical trials in critically ill children evaluated time from randomization to liberation from all forms of respiratory support as their primary outcome (33, 34) based on parental preference to have children free of respiratory support that would prevent them from holding, feeding, or otherwise interacting supportively. For intubated patients, extubation success, duration of mechanical ventilation, and mortality were three of the five core outcome set measures recommended for clinical trials in mechanical ventilation based on expert consensus using a rigorous methodology (35). LOS was another recommended core outcome set measure, which strongly correlates with CPS-Ped.

The application of CPS-Ped across three multicenter real-world pediatric cohorts hospitalized with severe viral infections is a major strength of our study. Our findings also have important limitations. First, our data were collected at specific time points, limiting our ability to conduct time-to-event analyses, which could be important metrics. Second, we did not assess long-term health outcomes such as decreases in lung function or neurocognitive sequelae, which occur in PARDS survivors (36–38). Third, although the WHO-CPS was developed by an international panel of experts, a similar Delphi process of pediatric experts was not conducted for CPS-Ped. Fourth, our analyses were limited to pediatric patients with influenza and COVID-19 infection and may not be applicable to other causes of pediatric acute respiratory failure. Fifth, our post hoc assessment of vasopressors showed score inflation in a small percentage of patients who otherwise would not have met clinical improvement criteria, which may be a result of how clinical improvement was defined. Sixth, potential drawbacks of using a composite outcome include potential interpretation challenges, increased complexity compared to mortality, and challenges with acceptance by regulatory agencies.

CONCLUSIONS

We modified the WHO-CPS for use in pediatric patients to capture the spectrum of illness severity and threshold for clinical improvement in acute respiratory failure. Applying CPS-Ped to real-world data from children with viral infections shows that CPS-Ped measures the progression of disease and recovery in patients with mild–moderate illness, whereas capturing meaningful improvement in those with a life-threatening disease. Clinical improvement by day 14 was correlated with hospital LOS, an indicator of recovery, and sample sizes appear feasible as a potential outcome measure. These promising findings support the future evaluation of CPS-Ped in clinical trials.

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REFERENCES

1. Burns JP, Sellers DE, Meyer EC, et al: Epidemiology of death in the PICU at five U.S. teaching hospitals*. *Crit Care Med* 2014; 42:2101–2108
2. Ibiebele I, Algert CS, Bowen JR, et al: Pediatric admissions that include intensive care: A population-based study. *BMC Health Serv Res* 2018; 18:264
3. Khemani R, Smith L, Lopez-Fernandez Y, et al: Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology (PARDIE): An international observational study. *Lancet Respir Med* 2019; 7:115–128
4. Gupta S, Sankar J, Lodha R, et al: Comparison of prevalence and outcomes of pediatric acute respiratory distress syndrome using pediatric acute lung injury consensus conference criteria and Berlin definition. *Front Pediatr* 2018; 6:93
5. Parvathaneni K, Belani S, Leung D, et al: Evaluating the performance of the pediatric acute lung injury consensus conference definition of acute respiratory distress syndrome. *Pediatr Crit Care Med* 2017; 18:17–25
6. Wong JJ, Jit M, Sultana R, et al: Mortality in pediatric acute respiratory distress syndrome: A systematic review and meta-analysis. *J Intensive Care Med* 2019; 34:563–571
7. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800

8. Matthay M, Zemans R, Zimmerman G, et al: Acute respiratory distress syndrome. *Nat Rev Dis Primers* 2019; 5:18
9. Thomas N, Jouvet P, Willson D: Acute lung injury in children—kids really aren't just "little adults." *Pediatr Crit Care Med* 2013; 14:429–432
10. Emeriaud G, López-Fernández YM, Iyer NP, et al; Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) Group on behalf of the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network: Executive summary of the second international guidelines for the diagnosis and management of pediatric acute respiratory distress syndrome (PALICC-2). *Pediatr Crit Care Med* 2023; 24:143–168
11. Ranieri VM, Rubenfeld GD, Thompson BT, et al; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin definition. *JAMA* 2012; 307:2526–2533
12. Yehya N, Thomas NJ: Relevant outcomes in pediatric acute respiratory distress syndrome studies. *Front Pediatr* 2016; 4:51
13. Yehya N, Harhay MO, Curley MAQ, et al: Reappraisal of ventilator-free days in critical care research. *Am J Respir Crit Care Med* 2019; 200:828–836
14. Villar J, Kacmarek RM: The APPS: An outcome score for the acute respiratory distress syndrome. *J Thorac Dis* 2016; 8:E1343–E1347
15. Bos LD, Schouten LR, Cremer OL, et al; MARS consortium: External validation of the APPS, a new and simple outcome prediction score in patients with the acute respiratory distress syndrome. *Ann Intensive Care* 2016; 6:89
16. Beigel JH, Aga E, Elie-Turenne MC, et al; IRC005 Study Team: Anti-influenza immune plasma for the treatment of patients with severe influenza A: A randomised, double-blind, phase 3 trial. *Lancet Respir Med* 2019; 7:941–950
17. Lee N, Smith SW, Hui DSC, et al: Development of an ordinal scale treatment endpoint for adults hospitalized with influenza. *Clin Infect Dis* 2021; 73:e4369–e4374
18. Beigel JH, Tomashek KM, Dodd LE, et al; ACTT-1 Study Group Members: Remdesivir for the treatment of COVID-19—final report. *N Engl J Med* 2020; 383:1813–1826
19. Marshall JC, Murthy S, Diaz J, et al: A minimal common outcome measure set for COVID-19 clinical research. *Lancet Infect Dis* 2020; 20:e192–e197
20. Nasir N, Mahmood F, Habib K, et al: Tocilizumab for COVID-19 acute respiratory distress syndrome: Outcomes assessment using the WHO ordinal scale. *Cureus* 2020; 12:e12290
21. Tomazini BM, Maia IS, Cavalcanti AB, et al; COALITION COVID-19 Brazil III Investigators: Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. *JAMA* 2020; 324:1307–1316
22. Khan AR, Misdary C, Yegya-Raman N, et al: Montelukast in hospitalized patients diagnosed with COVID-19. *J Asthma* 2021; 59:780–786
23. Ader F, Bouscambert-Duchamp M, Hites M, et al; DisCoVeRy Study Group: Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): A phase 3, randomised, controlled, open-label trial. *Lancet Infect Dis* 2022; 22:209–221
24. Ducharme-Crevier L, Essouri S, Emeriaud G: Noninvasive ventilation in pediatric intensive care: From a promising to an established therapy, but for whom, when why and how? *Pediatr Crit Care Med* 2015; 16:481–482
25. Schuster JE, Halasa NB, Nakamura M, et al; Overcoming COVID-19 Investigators: A description of COVID-19-directed therapy in children admitted to US intensive care units 2020. *J Pediatr Infect Dis Soc* 2022; 11:191–198
26. Hall M, Geyer S, Guo CY, et al: Innate immune function and mortality in critically ill children with influenza: A multicenter study. *Crit Care Med* 2013; 41:224–236
27. Olson SM, Newhams MM, Halasa NB, et al; Pediatric Intensive Care Influenza Investigators: Vaccine effectiveness against life-threatening influenza illness in US children. *Clin Infect Dis* 2022; 75:230–238
28. Feldstein LR, Rose EB, Horwitz SM, et al; Overcoming COVID-19 Investigators: Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med* 2020; 383:334–346
29. Feldstein LR, Tenforde MW, Friedman KG, et al; Overcoming COVID-19 Investigators: Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *JAMA* 2021; 325:1074–1087
30. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; 94:496–509
31. Andrist E, Nuppnau M, Barbaro R, et al: Association of race with pulse oximetry accuracy in hospitalized children. *JAMA Netw Open* 2022; 5:e224584
32. Sjoding M, Dickson R, Iwashyna T, et al: Racial bias in pulse oximetry measurements. *N Engl J Med* 2020; 383:2477–2478
33. Ramnarayan P, Richards-Belle A, Drikite L, et al; FIRST-ABC Step-Down RCT Investigators and the Paediatric Critical Care Society Study Group: Effect of high-flow nasal cannula therapy vs continuous positive airway pressure following extubation on liberation from respiratory support in critically ill children: A randomized clinical trial. *JAMA* 2022; 327:1555–1565
34. Ramnarayan P, Richards-Belle A, Drikite L, et al; FIRST-ABC Step-Up RCT Investigators and the Paediatric Critical Care Society Study Group: Effect of high-flow nasal cannula therapy vs continuous positive airway pressure therapy on liberation from respiratory support in acutely ill children admitted to pediatric critical care units: A randomized clinical trial. *JAMA* 2022; 328:162–172
35. Blackwood B, Ringrow S, Clarke M, et al: A core outcome set for critical care ventilation trials. *Crit Care Med* 2019; 47:1324–1331
36. Boucher V, Mathy C, Lacroix J, et al: Post-discharge respiratory outcomes of children with acute respiratory distress syndrome. *Pediatr Pulmonol* 2020; 55:468–473
37. Neve V, Sadik A, Petyt L, et al: Whole pulmonary assessment 1 year after paediatric acute respiratory distress syndrome: Prospective multicentre study. *Ann Intensive Care* 2022; 12:79
38. Watson RS, Beers SR, Asaro LA, et al; RESTORE-Cognition Investigators: Association of acute respiratory failure in early childhood with long-term neurocognitive outcomes. *JAMA* 2022; 327:836–845