The Use and Duration of Preintubation Respiratory Support Is Associated With Increased Mortality in Immunocompromised Children With Acute Respiratory Failure

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OBJECTIVES: To determine the association between preintubation respiratory support and outcomes in patients with acute respiratory failure and to determine the impact of immunocompromised (IC) diagnoses on outcomes after adjustment for illness severity.

DESIGN: Retrospective multicenter cohort study.

SETTING: Eighty-two centers in the Virtual Pediatric Systems database.

PATIENTS: Children 1 month to 17 years old intubated in the PICU who received invasive mechanical ventilation (IMV) for greater than or equal to 24 hours.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: High-flow nasal cannula (HFNC) or noninvasive positive-pressure ventilation (NIPPV) or both were used prior to intubation in 1,825 (34%) of 5,348 PICU intubations across 82 centers. When stratified by IC status, 50% of patients had no IC diagnosis, whereas 41% were IC without prior hematopoietic cell transplant (HCT) and 9% had prior HCT. Compared with patients intubated without prior support, preintubation exposure to HFNC (adjusted odds ratio [aOR], 1.33; 95% CI, 1.10–1.62) or NIPPV (aOR, 1.44; 95% CI, 1.20–1.74) was associated with increased odds of PICU mortality. Within subgroups of IC status, preintubation respiratory support was associated with increased odds of PICU mortality in IC patients (HFNC: aOR, 1.50; 95% CI, 1.11–2.03; NIPPV: aOR, 1.76; 95% CI, 1.31–2.35) and HCT patients (HFNC: aOR, 1.75; 95% CI, 1.07–2.86; NIPPV: aOR, 1.85; 95% CI, 1.12–3.02) compared with IC/HCT patients intubated without prior respiratory support. Preintubation exposure to HFNC/NIPPV was not associated with mortality in patients without an IC diagnosis. Duration of HFNC/NIPPV greater than 6 hours was associated with increased mortality in IC HCT patients (HFNC: aOR, 2.41; 95% CI, 1.05–5.55; NIPPV: aOR, 2.53; 95% CI, 1.04–6.15) and patients compared HCT patients with less than 6-hour HFNC/NIPPV exposure. After adjustment for patient and center characteristics, both preintubation HFNC/NIPPV use (median, 15%; range, 0–63%) and PICU mortality varied by center.

CONCLUSIONS: In IC pediatric patients, preintubation exposure to HFNC and/or NIPPV is associated with increased odds of PICU mortality, independent of illness severity. Longer duration of exposure to HFNC/NIPPV prior to IMV is associated with increased mortality in HCT patients.

KEY WORDS: acute respiratory failure; hematopoietic cell transplantation; high-flow nasal cannula; immunocompromised status; noninvasive ventilation; pediatric critical care

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High-flow nasal cannula (HFNC) and noninvasive positive-pressure ventilation (NIPPV) are commonly employed in the initial management of children with acute respiratory failure to provide a higher level of respiratory support without the adverse effects of invasive mechanical ventilation (IMV) (1–3). HFNC and NIPPV improve gas exchange and decrease work of breathing in respiratory failure, allowing many children to recover without IMV (4–7). However, recent data suggest that the 25–30% of children who fail HFNC/NIPPV may be at higher risk of worse outcomes than patients who receive IMV as the initial therapy (8–10) and that this risk may be influenced by patient factors (11–13).

The management of acute respiratory failure in children with immunocompromised (IC) status and history of hematopoietic cell transplant (HCT) may warrant special consideration. We have previously identified an increased risk of sepsis-related mortality associated with IC and HCT status (14). In that report, IC and HCT patients had higher rates of respiratory failure and were more likely to be hospitalized prior to their acute deterioration than patients without IC diagnoses (14). A recent analysis of pediatric HCT patients with respiratory failure identified an alarming rate of cardiac arrest at the time of tracheal intubation for patients with preintubation exposure to NIPPV (12). Longer PICU length of stay prior to intubation has been associated with increased mortality in HCT patients (15), whereas earlier NIPPV has been associated with increased mortality in IC patients (16). In the absence of clinical trial data to support the use of HFNC/NIPPV in IC and HCT patients with acute respiratory failure, observational data to guide clinical decision-making regarding the timing and mode of noninvasive support are essential to help intensivists manage these high-risk patients.

We have previously used diagnosis and procedural codes from the multicenter Virtual Pediatric Systems (VPS, LLC) database to accurately phenotype IC diagnoses and history of HCT in patients with sepsis (14). In the present study, we identify a large, multicenter cohort of patients who underwent tracheal intubation, assess the prevalence of IC diagnoses among these patients, determine the association between preintubation respiratory support and PICU mortality, and identify center-level variation of patient outcomes after adjustment for demographics and illness severity. We hypothesized that preintubation respiratory support would be associated with increased PICU mortality in a time-dependent manner for all patients included in the analysis, that PICU mortality would vary by IC status, and that patient outcomes would vary by center.

MATERIALS AND METHODS

We conducted a retrospective observational cohort study using the multicenter VPS database after review by the Children's Hospital of Philadelphia Institutional Review Board (20-018107). All patient records in the VPS database during the study period (from January 1, 2014, to December 31, 2019) were queried for a procedure code for endotracheal intubation, a required data field for all participating VPS sites. For patients with multiple intubations, only the first intubation after PICU admission was included for analysis. Patients aged less than 1 month or greater than or equal to 18 years at PICU admission were excluded, as well as patients with tracheostomy and those with home noninvasive or invasive ventilatory support. We excluded patients who were intubated outside of the PICU, as well as patients who received IMV for less than 24 hours. Patients from low-volume centers that reported less than or equal to 10 intubations during the study period were also excluded.

Exposure and Outcomes

All available data were extracted from the VPS database, including demographic information, source of admission, coded diagnoses and procedures, Pediatric Index of Mortality (PIM)-2 (17) severity of illness data, length of stay, and clinical outcome. The primary outcome was all-cause PICU mortality, which is reported by all participating centers. The primary exposure was use of HFNC and/or NIPPV prior to endotracheal intubation; for patients with sequential exposures to both modes of support, the final mode of support prior to intubation was defined as the exposure. We defined these exposures based on procedure codes for HFNC, continuous positive airway pressure, and bilevel positive airway pressure; these procedures are required variables and indicate the timing and duration of exposure. IC status was defined by the *International Classification of Diseases*, 9th Edition code (**eTable 1**, http://links.lww.com/CCM/H86) (14) and classified as

a trichotomous exposure in our analysis (no IC diagnosis vs IC without HCT vs HCT). Identified IC diagnoses included malignancy, solid organ transplant, congenital immunodeficiency, hemophagocytic lymphohistiocytosis, and aplastic anemia.

Statistical Analyses

Differences in baseline patient characteristics, IC diagnoses, and exposure to HFNC and NIPPV were analyzed by Wilcoxon rank-sum test or Kruskal-Wallis test as appropriate for continuous variables and χ^2 test for categorical variables. To measure the association of mortality with preintubation exposure to HFNC/NIPPV and evaluate variation in PICU mortality across centers, we constructed mixed-effect (ME) logistic regression models using a series of a priori defined patient factors and center factors known to be associated with mortality. We additionally tested for variance in rates of asthma and sepsis across IC diagnoses. Because rates of sepsis varied by IC status, we completed a post hoc sensitivity analysis incorporating sepsis diagnosis into the model. Exposure to HFNC or NIPPV was modeled as a single categorical variable. IC diagnoses were also modeled as a single categorical variable; HCT was modeled as an effect modifier based on our prior study of sepsis-related mortality in HCT patients (14). The base ME model included no fixed effects and only a center-level random effect; the estimated variance of the random effect reflected the magnitude of the mortality variation across hospitals. In this model, a significant test of variance greater than 0 suggests that the center-level variation is statistically significant. We subsequently added HFNC/NIPPV exposure, IC diagnoses, and a priori patient factors previously associated with PICU mortality—age, sex, and PIM-2 score—to this model as fixed effects to assess if the variance of the center-level random effect remained significant. Finally, we added a center-level variable defining the mean monthly volume of intubations (independent of IC status) to the model as a fixed effect to assess the contribution of center volume to center-level variance in PICU mortality.

We also conducted a secondary analysis to assess PICU mortality based on duration of preintubation exposure to HFNC and NIPPV. In this analysis, we first determined the PICU mortality by quintiles of HFNC/NIPPV duration and assessed the ordinal trend in mortality within each IC subgroup using the Cuzick test of trend. Noting a time-dependent effect on mortality, we then dichotomized patients based on a 6-hour duration of HFNC/NIPPV exposure, with the rationale that a 6-hour observation time represented a clinically meaningful trial of preintubation respiratory support. A similar 6-hour observation time period has also been used to assess response to pediatric acute respiratory distress syndrome therapies in the Pediatric Acute Respiratory Distress syndrome Incidence and Epidemiology (PARDIE) study (18). We then constructed two separate ME models restricted to only patients with HFNC and NIPPV exposures, respectively, adjusted for the same fixed and random effects as the primary model. Analyses were performed using Stata/IC 15.1 (StataCorp, College Station, TX) with statistical significance defined as $p < 0.05$.

RESULTS

Characteristics of Patients Who Require Tracheal Intubation

During the study period, we identified 5,348 patients who met inclusion criteria across 82 centers (see **eFigure 1**, http://links.lww.com/CCM/H86, for details of the study population). Of patients requiring IMV, 34% (1,825/5,348) were exposed to HFNC/NIPPV prior to intubation. IC and/or HCT diagnoses were identified in 49% of patients (2,638/5,348) and 59% of nonsurvivors (682/1,148). Demographics, patient characteristics, and clinical outcomes are shown in **Table 1**, stratified by IC diagnoses. As expected, age, PIM-2 score, source of admission, sepsis prevalence, limitations of technological support, and rate of preintubation respiratory support all varied by IC status (all $p < 0.001$).

Association Between Mode of Respiratory Support and PICU Mortality

For our primary analysis, we measured the association between preintubation modes of respiratory support with PICU mortality using an ME logistic regression model. We built the model starting with a center-level random effect and added the following fixed effects: age, sex, PIM-2 score, and center-level volume of intubations per month. In this preliminary model, preintubation exposure to HFNC (adjusted odds ratio [aOR], 1.33; 95% CI, 1.10–1.62) and NIPPV (aOR, 1.44; 95% CI, 1.20–1.74) were associated with an increased odds of PICU mortality compared with patients intubated without prior respiratory support. We then added history of IC

diagnoses and history of HCT to the model; results of this final ME model are shown in **Table 2**. Among IC patients without a history of HCT, preintubation exposure to HFNC (aOR, 1.50; 95% CI, 1.11–2.03) and NIPPV (aOR, 1.76; 95% CI, 1.31–2.35) conferred an increased odds of PICU mortality compared with IC patients without preintubation respiratory support. Among HCT patients, preintubation HFNC (aOR, 1.75; 95% CI, 1.07–2.86) and NIPPV (aOR, 1.85; 95% CI, 1.12–3.02) exposure was associated with an increased odds of mortality compared with HCT patients without preintubation respiratory support. Because rates of sepsis varied by cohort, we conducted a post hoc sensitivity analysis incorporating sepsis diagnosis into the model, which revealed similar findings to the above analysis; results are shown in **eTable 2** (http://links.lww.com/CCM/H86).

TABLE 1.

Baseline Characteristics of Patients Who Required Tracheal Intubation, by Immunocompromised Status

Variable	No IC Diagnosis (*n* = 2,710)	IC, Not HCT (*n* = 2,179)	HCT (*n* = 459)	*p*[a]
Age distribution, *n* (%)				
1–23 mo	1,588 (59)	529 (24)	142 (31)	< 0.001
2–5 yr	414 (15)	559 (26)	98 (21)	
6–12 yr	335 (12)	574 (26)	104 (23)	
13–18 yr	373 (14)	517 (24)	115 (25)	
Male sex, *n* (%)	1,474 (54)	1,174 (54)	249 (54)	0.51
Race, *n* (%)				
American Indian/Alaska Native	36 (1)	24 (1)	1 (< 1)	< 0.001
Asian	96 (4)	120 (5)	11 (2)	
Black or African American	484 (18)	274 (13)	54 (12)	
Hawaiian or Pacific Islander	12 (< 1)	3 (< 1)	0 (0)	
Hispanic or Latino	353 (13)	342 (16)	49 (11)	
White	1,226 (45)	976 (45)	157 (34)	
Other/Unspecified	503 (19)	440 (20)	187 (41)	
Pediatric Index of Mortality-2 probability of death, median (interquartile range)	1.42 (0.85–4.84)	2.91 (0.91–4.97)	4.13 (1.05–5.68)	< 0.001
Admission source, *n* (%)				
Emergency department	1,193 (44)	556 (26)	39 (9)	< 0.001
Hospital ward	1,062 (39)	1,306 (60)	392 (85)	
Operating room	244 (9)	180 (8)	16 (3)	
Other	211 (8)	137 (6)	12 (3)	
Severe sepsis/septic shock, *n* (%)	387 (14)	456 (21)	173 (38)	< 0.001
Asthma diagnosis, *n* (%)	208 (8)	138 (6)	38 (8)	0.12
Limitations of care, *n* (%)[b]	230/2,305 (10)	249/1,933 (13)	95/402 (24)	< 0.001
Preintubation support, *n* (%)				
None	1,731 (64)	1,547 (70)	245 (53)	< 0.001
High-flow nasal cannula	444 (16)	315 (15)	114 (25)	
Noninvasive positive-pressure ventilation	535 (20)	317 (15)	100 (22)	

HCT = hematopoietic cell transplant, IC = immunocompromised.

[a]Kruskal-Wallis *H* test for continuous variables and χ^2 test for categorical variables, $\alpha = 0.05$.

[b]Limitations of care data were unavailable for 16% of study participants (no IC diagnosis: 19%; IC, not HCT: 14%; HCT: 13%).

TABLE 2.
Adjusted Odds of PICU Mortality, Stratified Based on Preintubation Exposure to Respiratory Support

Preintubation Respiratory Support	No IC Diagnosis, aOR (95% CI)[a]	IC, Not HCT, aOR (95% CI)[a]	HCT, aOR (95% CI)[a]
None	Reference	Reference	Reference
High-flow nasal cannula	0.95 (0.70–1.29)	1.50 (1.11–2.03)	1.75 (1.07–2.86)
Noninvasive positive pressure ventilation	1.03 (0.78–1.36)	1.76 (1.31–2.35)	1.85 (1.12–3.02)

aOR = adjusted odds ratio, HCT = hematopoietic cell transplant, IC = immunocompromised.
[a]Mixed-effects model, adjusted for patient-level fixed effects (IC diagnosis, age, gender, and Pediatric Index of Mortality-2 score) and center-level fixed effects (mean monthly volume of tracheal intubations). For each category of IC status, patients intubated without preintubation exposure to high-flow nasal cannula/noninvasive positive-pressure ventilation serve as the reference group.

Association Between Duration of Respiratory Support and PICU Mortality

Our analysis of preintubation respiratory support as a time-dependent exposure included primary stratification into quintiles of duration of HFNC and NIPPV exposure, as shown in **Figure 1**. In this analysis, the relationship between exposure duration and outcome varied by IC diagnosis. Among HCT patients, mortality increased across quintiles of duration of exposure to HFNC ($p = 0.002$) and NIPPV ($p = 0.043$). This time-dependent effect was not seen in IC patients without HCT or in patients without IC diagnosis. We also noted a bimodal distribution of mortality associated with duration of NIPPV exposure in patients without HCT.

We further dichotomized patients based on a 6-hour duration of HFNC/NIPPV exposure and tested the association between duration HFNC and NIPPV exposures and PICU mortality, adjusted for the same fixed and random effects as the primary model. As shown in **Table 3**, HCT patients had an increased odds of mortality associated with greater than 6-hour duration of preintubation HFNC (aOR, 2.41; 95% CI, 1.05–5.55) and NIPPV (aOR, 2.53; 95% CI, 1.04–6.15) exposure compared with HCT patients with duration of exposure less than or equal to 6 hours. Longer duration of HFNC/NIPPV exposure was not associated with increased mortality in IC patients without HCT or in patients without an IC diagnosis.

Center-Level Variance in PICU Mortality

Preintubation HFNC/NIPPV use and PICU mortality varied significantly across the 82 centers in this study. Preintubation HFNC use by center varied from 0% to 55% (median 14%), and preintubation NIPPV use by center varied from 0% to 63% (median 15%). To evaluate center-level variance in PICU mortality, we constructed two independent ME models—for preintubation HFNC and NIPPV exposure—and used stepwise addition of patient- and center-level fixed effects to our model. Center-level variance was significant in the base ME models. The addition of preintubation respiratory support, IC diagnoses, and patient factors (age, sex, and PIM-2 score) to the model decreased center-level variance in PICU mortality, but this variance remained significant in both models ($p < 0.001$). The subsequent addition of duration of preintubation respiratory support and mean monthly volume of intubations further decreased this variance, which remained statistically significant in both models ($p < 0.001$).

Figure 2 displays the adjusted PICU mortality rate by center for patients with preintubation exposure to HFNC and NIPPV, with stepwise adjustment for patient-level and center-level fixed effects. The median odds ratio that quantifies the heterogeneity of outcomes between the centers (19) is displayed for each successive model. For both modes of preintubation respiratory support, addition of patient-level and center-level factors to the model reduces, but does not eliminate the heterogeneity of outcomes, suggesting that unmeasured institutional characteristics also contribute to center-level variance in PICU mortality.

DISCUSSION

This large, multicenter cohort study was designed to evaluate the association between preintubation respiratory support and PICU mortality in IC children.

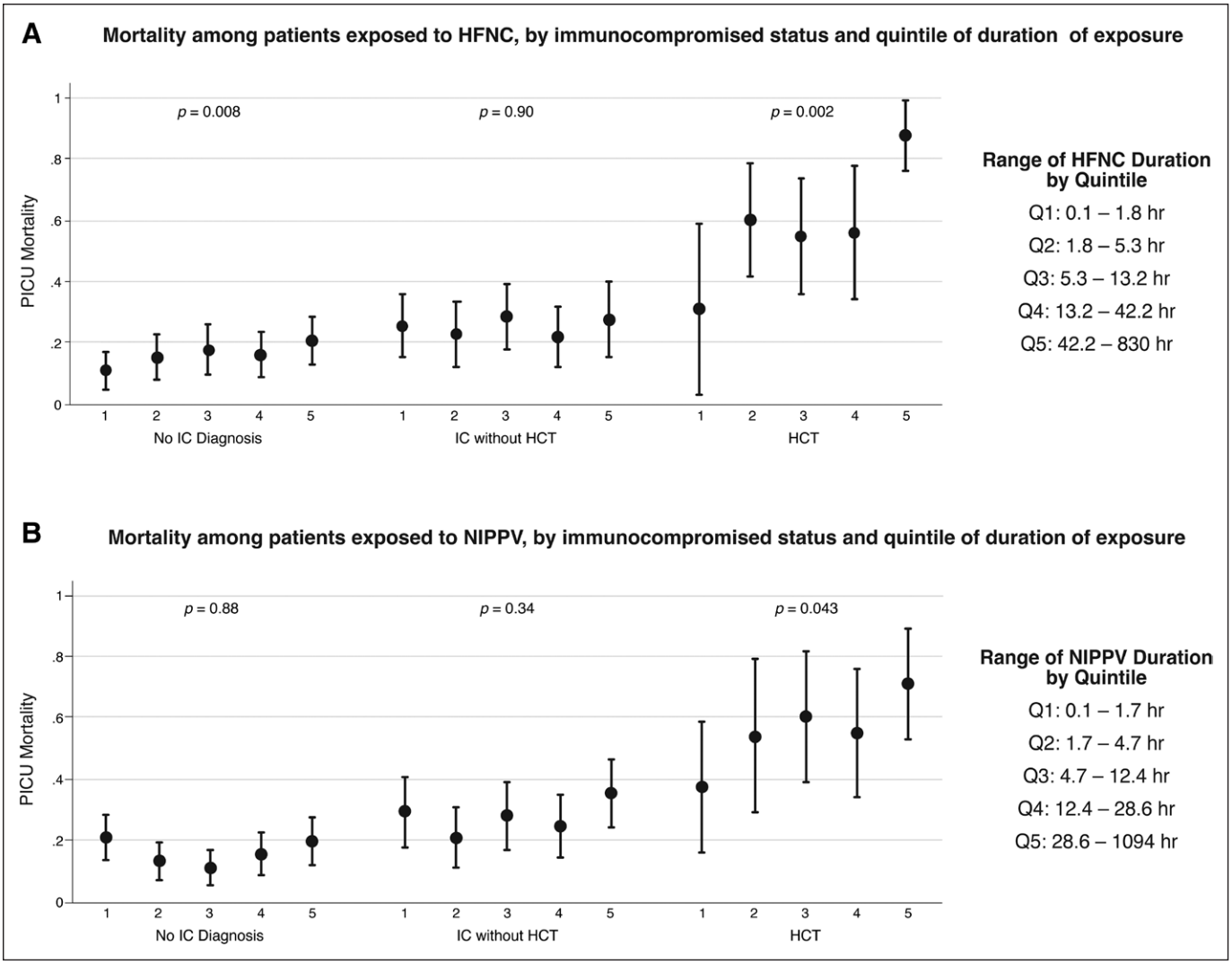

Figure 1. Association between duration of respiratory support and PICU mortality. PICU mortality by quintiles of high-flow nasal cannula (HFNC) (**A**) and noninvasive positive-pressure ventilation (NIPPV) (**B**) duration, stratified by immunocompromised (IC) diagnoses. For each quintile, the *center circle* represents the quintile mortality rate, and the *bars* represent the 95% CI around this mortality rate. The Cuzick test of trend was used to assess the ordinal trend in mortality within each IC subgroup. HCT = hematopoietic cell transplant.

Using a well-defined cohort of patients from the VPS database, we found that preintubation exposure to HFNC or NIPPV was associated with increased odds of PICU mortality, a finding that aligns with a recent report from the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study (20). When we further stratified this risk by IC diagnoses, we discovered that this association was driven by patients with IC diagnoses or HCT, as an increased odds of mortality was no longer seen in the patients without IC diagnoses after adding these exposures to our models. By assessing preintubation respiratory support as a time-dependent exposure, we demonstrated that IMV after a prolonged exposure to HFNC/NIPPV was associated with increased mortality in HCT patients. Finally, we demonstrated substantial variation in PICU mortality across centers in children with preintubation exposure to HFNC/NIPPV, even after adjustment for severity of illness, IC status, and center volume.

Our primary analysis yields several novel insights into specific IC phenotypes relevant to clinicians and clinical researchers. First, IC diagnoses are very common among children with respiratory failure who require IMV, present in 49% of the cohort and 59% of PICU mortalities. Second, our results confirm that a history of HCT is a major risk factor for PICU mortality among patients with acute respiratory failure.

TABLE 3.
Adjusted Odds of PICU Mortality, Based on Duration of Preintubation Respiratory Support

Preintubation HFNC Exposure		Preintubation NIPPV Exposure	
IC Status + Duration	**aOR (95% CI)[a]**	**IC Status + Duration**	**aOR (95% CI)[b]**
No IC Dx		No IC Dx	
HFNC ≤ 6 hr ($n = 194$)	Reference	NIPPV ≤ 6 hr ($n = 262$)	Reference
HFNC > 6 hr ($n = 250$)	1.44 (0.83–2.53)	NIPPV > 6 hr ($n = 273$)	0.91 (0.56–1.48)
IC, not HCT		IC, not HCT	
HFNC ≤ 6 hr ($n = 134$)	Reference	NIPPV ≤ 6 hr ($n = 135$)	Reference
HFNC > 6 hr ($n = 181$)	0.83 (0.49–1.43)	NIPPV > 6 hr ($n = 182$)	1.19 (0.70–2.04)
HCT		HCT	
HFNC ≤ 6 hr ($n = 44$)	Reference	NIPPV ≤ 6 hr ($n = 36$)	Reference
HFNC > 6 hr ($n = 70$)	2.41 (1.05–5.55)	NIPPV > 6 hr ($n = 64$)	2.53 (1.04–6.15)

aOR = adjusted odds ratio, Dx = diagnosis, HCT = hematopoietic cell transplant, HFNC = high-flow nasal cannula, IC = immunocompromised, NIPPV = noninvasive positive-pressure ventilation.

[a]Mixed-effects model, adjusted for patient-level fixed effects (IC diagnosis, age, gender, and Pediatric Index of Mortality-2 [PIM-2] score) and center-level fixed effects (mean monthly volume of tracheal intubations), restricted to patients who received HFNC prior to tracheal intubation. For each category of IC status, patients intubated without preintubation exposure to HFNC serve as the reference group.

[b]Mixed-effects model, adjusted for patient-level fixed effects (IC diagnosis, age, gender, PIM-2 score) and center-level fixed effects (mean monthly volume of tracheal intubations), restricted to patients who received NIPPV prior to tracheal intubation. For each category of IC status, patients intubated without preintubation exposure to NIPPV serve as the reference group.

These findings are congruent with recent reports that have identified high levels of morbidity and mortality associated with respiratory failure and sepsis in pediatric HCT patients (12, 14, 21). The increased risk associated with HCT status is likely multifactorial (22), conferred by prolonged T cell immunosuppression (23), lung injury due to conditioning regimens and peritransplant alloimmune disease (24), and increased exposure to infectious agents (25). Third, we found that in the absence of IC diagnosis or HCT, exposure to preintubation respiratory support is not associated with an increased odds of PICU mortality. Because patient immune status has a major impact on clinical outcomes in this cohort, careful consideration of IC diagnoses will be important in the design of future trials to identify best practices regarding noninvasive management of pediatric respiratory failure. Finally, we have identified a variable association between duration of preintubation respiratory support and clinical outcomes based on IC diagnoses. Although longer duration of exposure is associated with increased PICU mortality in select populations, it will be important for future, prospective studies to evaluate physiologic criteria that predict success/failure during a time-limited trial of noninvasive support in pediatric respiratory failure.

In our primary analysis, we identified IC status as an important risk factor for mortality in pediatric respiratory failure. Importantly, we also identified that mode and duration of preintubation respiratory support do not convey an increased risk of PICU mortality in patients without an IC diagnosis. Although some prior studies have collected limited data regarding IC diagnoses (20, 26), our results indicate that subgroups of IC and HCT patients may be responsible for the increased risk associated with preintubation respiratory support. Based on our findings, we recommend that future trials of pediatric acute respiratory failure stratify patients based on IC and HCT status to accurately account for the impact of these conditions on relevant patient outcomes.

We found that PICU mortality varied significantly across the 82 centers in our cohort. Although some variance was explained by patient-level factors, including IC diagnoses and illness severity scores, as well as the center-level volume of intubations, significant variance among centers remained after both

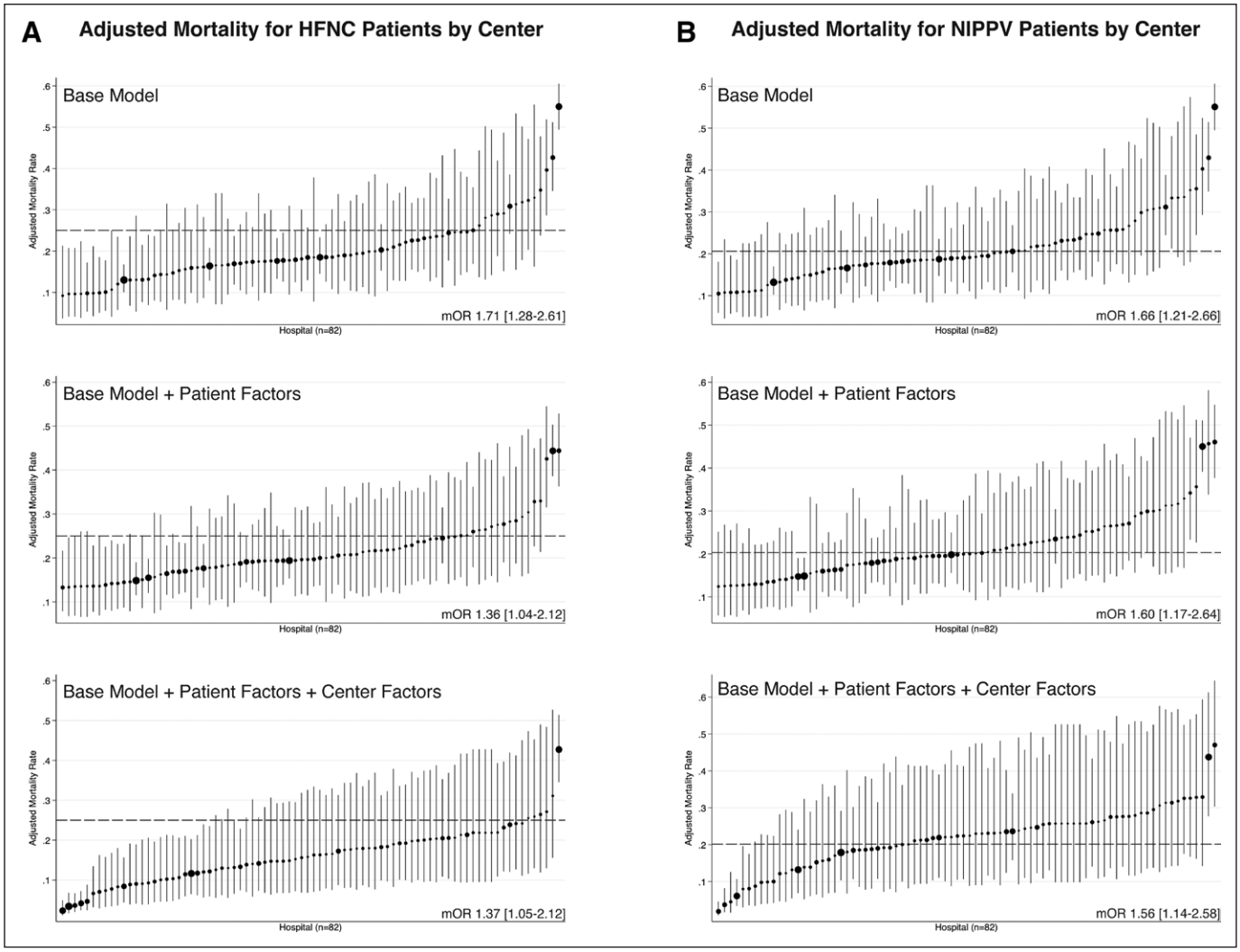

Figure 2. Center-level variation in PICU mortality. Center-level variation in adjusted PICU mortality for patients with preintubation exposure to high-flow nasal cannula (HFNC) (**A**) or noninvasive positive-pressure ventilation (NIPPV) (**B**). For **A** and **B**, the graphs show adjusted mortality in the base model (*Top*), the base model + patient factors (*Middle*), and the base model + patient factors + center volume (*Bottom*). The size of the point estimate corresponds to the volume of patients from each participating hospital. *Error bars* indicate the 95% CI. The adjusted mortality rate for the entire cohort is indicated by a *broken line* on each graph, and the median odds ratio (mOR) is indicated at the *lower right corner*.

adjustments. Substantial variability in the use and duration of HFNC/NIPPV in pediatric respiratory failure has been previously reported (27–29). Our results suggest that this variation in care practices may be associated with differences in patient outcomes, although other unmeasured causes of patient- and center-level variance may also influence this finding. These data, combined with similar recent data showing increased mortality associated with preintubation NIPPV use in the RESTORE trial (20), suggest a strong rationale for a prospective study of noninvasive respiratory support in pediatric acute respiratory failure.

Although retrospective studies of pediatric critical illness have inherent limitations, our study has several notable strengths. We have previously demonstrated that the multicenter VPS dataset can be used to identify an accurate cohort of IC patients (14), and in the present analysis, we have leveraged that cohort to yield important new insights into PICU mortality among IC patients with respiratory failure who require intubation and IMV. Unlike administrative datasets, data in VPS are extracted by expert, trained coders according to standard data definitions subject to quarterly interrater reliability testing. This dataset also includes required reporting of PICU procedures and robust severity of illness data, which allows for careful selection and adjustment for covariates. Despite these strengths, there are important limitations that must

be considered when interpreting these results. IC phenotypes were identified by diagnosis code, and thus, no information regarding current disease status, severity of clinical phenotype, stage of malignancy, and concurrent disease-modifying therapies was available for analysis. Due to this data limitation, we were also unable to identify and assess patients who are IC due to chronic immunosuppressive therapies, and IC phenotypes could not be confirmed with clinical criteria. The timing and indications for HCT, conditioning regimen, transplant type, source of cells, and transplant-related complications are unavailable in VPS. Inclusion of these variables would allow for further in-depth risk stratification of these high-risk patients. Furthermore, data regarding the etiology of respiratory failure are largely unavailable in VPS, thus limiting our ability to assess confounding by indication. Because VPS only reports data starting from PICU admission, we are unable to quantify the duration of HFNC/NIPPV exposure prior to PICU admission. This information bias may have underestimated the duration of preintubation support in some patients admitted from an inpatient ward and could also impact clinical outcomes if patients were inadequately supported prior to PICU admission. Code status is only recorded in VPS from PICU admission, which limits our ability to account for dynamic discussions regarding limitations of technological support, which often occur in a rapidly deteriorating patient. Finally, because our study question was limited to patients who required endotracheal intubation, we cannot comment on the role of HFNC/NIPPV in patients who successfully recover without the need for IMV.

CONCLUSIONS

In this large, multicenter study of noninvasive respiratory support prior to tracheal intubation, IC diagnoses were present in 49% of patients who required tracheal intubation and 59% of nonsurvivors. After adjustment for measured confounders, exposure to HFNC and NIPPV prior to intubation was associated with an increased odds of mortality in IC and HCT patients, but not among patients without an IC diagnosis. Increased duration of preintubation HFNC/NIPPV was also associated with increased PICU mortality in HCT patients. As expected, there was significant variation in PICU mortality among centers.

As our understanding of optimal care practices for pediatric respiratory failure continues to develop, we must pay careful attention to the high-risk cohort of children with IC conditions. We recommend that IC patients should be rapidly reassessed after introduction of HFNC/NIPPV, as patients who require IMV after HFNC/NIPPV appear to have increased mortality. Further research into the appropriate duration and mode of support for IC and HCT patients with respiratory failure is critical to improving survival in this heterogeneous, high-risk cohort of patients. The presence of substantial variation in use of HFNC/NIPPV and PICU outcomes across centers highlights the need for a prospective study of best practices regarding noninvasive support in pediatric acute respiratory failure, with particular attention to patients with prior HCT.

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