ABSTRACT: We propose a novel metric evaluating the impact an exposure to a large positive fluid balance over time has on clinical outcomes in children with respiratory failure, termed “fluid overload mechanically ventilated” (FOMV) days. We performed a retrospective cohort study of mechanically ventilated children. Using multivariable regression analyses, each FOMV day was associated with a 5% decreased likelihood of having a ventilator-free day (adjusted incidence rate ratio [aIRR] , 0.95; 95% CI, 0.95–0.96), a 5% increased likelihood of having an additional day of stay (aIRR, 1.05; 95% CI 1.05–1.06), and a 6% increased relative risk of death (aRR, 1.06; 95% CI, 1.01–1.11). FOMV is a novel exposure measure in children with acute respiratory failure associated with poor outcomes paralleling published data demonstrating dose-dependent exposure to a positive fluid balance is associated with worse outcomes. FOMV is a targetable exposure metric for future use in quality improvement initiatives and research studies that may help to determine the efficacy of interventions.

KEY WORDS: acute kidney injury; fluid overload; pediatric critical care; quality improvement

To the Editor:

A positive fluid balance is common in critically ill children and is associated with increased morbidity and mortality (1–4). Awareness of this phenomenon is increasing; however, there are no well-established real-time measures incorporating the dose-dependent and time-related relationship between positive fluid balance and clinical outcomes in high-risk patients. Several studies demonstrate mechanically ventilated patients with a greater than or equal to 10% positive fluid balance are associated with higher mortality, longer lengths of stay (LOS), and fewer ventilator-free days (VFDs) (1–3, 5). For these reasons, we propose a new measure to evaluate the impact an exposure to a large positive fluid balance over time has on clinical outcomes in children with respiratory failure, we term “fluid overload mechanically ventilated (FOMV) days.” This study aimed to validate FOMV days as a novel real-time fluid exposure measure in children with acute respiratory failure and determine its association with clinical outcomes.

METHODS

We performed a retrospective cohort study of all mechanically ventilated patients admitted to the PICU at Ann & Robert H. Lurie Children’s Hospital of Chicago between November 1, 2019, and February 1, 2022. Patients with a primary cardiac diagnosis or a history of congenital heart disease were excluded as they are admitted to a separate cardiac unit. We excluded patients with tracheostomies to focus on patients with acute respiratory failure. This study was...
performed in accordance with ethical standards of the Ann & Robert H. Lurie Children's Hospital Institutional Review Board (IRB) and with the Helsinki Declaration of 1975 and was submitted for review (IRB 2020-3691 “Optimizing Total Fluid Orders to Reduce Fluid Overload for Children Admitted to the ICU: A Quality Improvement Study” April 4, 2020) and exempt from human subjects' research. All data were extracted from the electronic health record using structured data queries.

 Definitions

Percent fluid balance was calculated using a weight-based approach (6–9):

\[
\text{Percent Fluid Balance} = \left( \frac{\text{Current Weight (kg)} - \text{PICU Admission Weight (kg)}}{\text{PICU Admission Weight (kg)}} \right) \times 100\%
\]

A FOMV day was defined as any calendar day in which the patient had both a greater than or equal to 10% positive fluid balance and was mechanically ventilated.

Standard practice in our PICU is to perform daily weights on all ventilated patients and to have a total fluid order as well to set a personalized goal of continuously administered fluids. In our dataset, when no weight was recorded for a day, the weight from the day immediately prior was carried forward. This assumption was made to be a conservative estimation of true FOMV days and any associations with clinical outcomes as the patients least likely to be weighed are those with a higher severity of illness, early in their stay.

Outcomes

The primary outcome was VFDs at 28 days. Secondary outcomes included in-hospital mortality and hospital LOS.

Statistical Analysis

All data analysis was performed using STATA 14 (StataCorp LP, College Station, TX). Statistical significance level was set at a two-sided alpha less than 0.05. Wilcoxon rank sum and chi-square tests were used to compare all continuous variables and categorical variables, respectively. Negative binomial regression analyses were performed to evaluate the association between FOMV days and VFD at 28 days and LOS in days. Modified Poisson regression analysis with robust error variance was performed to determine the association between FOMV days and mortality (10). To better establish the dose-dependent impact, these regression analyses were repeated with the FOMV days stratified into 0, 1–2, 3–7, and greater than 7 days. This decision was made with consideration of the expected timing of fluid balance using the Resuscitation, Optimization, Stabilization, Evacuation paradigm (11). Kruskal-Wallis and chi-square tests were used to compare continuous and categorical variables, respectively. All regression analyses were adjusted for a priori determined covariables of age, severity of illness at admission using the Pediatric Risk of Mortality (PRISM) III score, sex, and immunocompromised state. Immunocompromised state was defined as a diagnosis of malignancy or a history of stem cell or solid organ transplantation (12). A landmark day sensitivity analysis was performed to help ensure any association between FOMV days with VFD was not due to the ventilator day inherent to the definition of each FOMV day. This sensitivity analysis was done by repeating the negative binomial regression analysis with the same confounding variables and only including patients who required mechanical ventilation for the entirety of the first 3 days of the PICU stay. We evaluated the associations between the FOMV days only during the first 3 days (i.e., anywhere from 0 to 3 FOMV days) with VFD for the stay.

RESULTS

The study population included 672 patients. Of these, 43% were female with a median age of 3.5 years (interquartile range [IQR], 0.7–11.4 yr), a mortality rate of 7.6% (n = 51), a median LOS of 14.9 days (IQR, 6.9–25.6 d), and a median peak percent fluid balance of 8% (IQR, 3–14.5%). Daily weights were completed for 89.6% of the ventilated days. The peak fluid balance occurred on PICU days 1–2, 6.1% of the time; days 3–7, 28.7% of the time; and on days greater than 7, 65.2% of the time. Complete demographic and clinical outcomes are presented in Table 1.

After adjusting for covariates, each FOMV day was associated with a 5% decreased likelihood of having a VFD (incidence rate ratio [IRR], 0.95; 95% CI, 0.95–0.96), a 6% increased likelihood of having an additional day of stay (IRR, 1.06; 95% CI, 1.04–1.08), and a 6% increased relative risk of mortality (RR, 1.06; 95% CI, 1.01–1.11). We evaluated a possible interaction...
between PRISM III scores and FOMV days, and there was no effect modification by PRISM III in the final model.

When FOMV days were stratified into 0, 1–2, 3–7, and greater than 7 days, the VFDs were 25 (21–27) for 0 FOMV days, 22 (19–24) for 1–2 FOMV days, 21 (17–24) for 3–7 FOMV days, and 14 (5–18) for greater than 7 FOMV days (p < 0.0001). Mortality in each FOMV stratum was 4.7%, 9.4%, 12.4%, and 14.7% (p < 0.0001). Median LOS and interquartile range in days in each FOMV stratum was 10.9 (5.4–21), 17 (9.3–25.6), 17.9 (9.7–30.4), and 28 (19.5–44) (p < 0.0001). Table 2 describes the unadjusted and adjusted regression models based on these strata.

In the sensitivity analysis (landmark analysis of the first 3 d), 396 patients were included with a median VFD of 21 days (IQR 16–24 d), mortality rate of 9.6% (n = 38), and a median LOS of 17.9 days (IQR, 9.7–27.7 d). After adjusting for the covariates, each FOMV in the first 3 days was associated with a 3% decreased likelihood of having a VFD (aIRR, 0.97; 95% CI, 0.93–1.00). Table 2 demonstrates the unadjusted and adjusted IRR.

**DISCUSSION**

In this letter, we derive a novel exposure measure, FOMV days. In our study, FOMV days are associated with increased morbidity and mortality in a dose-dependent fashion. After adjusting for covariates, each day a patient had both greater than or equal to 10% positive fluid balance and mechanical ventilation was associated with a 5% decrease in the likelihood of having a VFD, a 6% increase in the likelihood of having an additional day in the hospital, and a 6% increase risk of death. Furthermore, the landmark sensitivity analysis shows the clinical impact from a FOMV is not solely related to an additional ventilator day inherent to the definition.

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**TABLE 1. Demographics and Outcomes**

| Variables                          | Total, N = 672 | Survivors, N = 621 | Nonsurvivors, N = 51 | p     |
|-----------------------------------|---------------|--------------------|----------------------|-------|
| Age (yr)                          | 3.5 (0.7–11.4)| 3.4 (0.7–10.9)     | 9.0 (0.4–15.2)       | 0.12  |
| Sex (female)                      | 43.3 (291)    | 43 (267)           | 47.1 (24)            | 0.57  |
| Primary admission diagnosis       |               |                    |                      |       |
| Respiratory failure               | 53.4 (359)    | 53.5 (332)         | 52.9 (27)            |       |
| Neurologic                        | 15.3 (103)    | 15.1 (94)          | 17.7 (9)             |       |
| Trauma                            | 4.8 (32)      | 4.4 (27)           | 9.8 (5)              |       |
| Postoperative                     | 12.1 (81)     | 12.9 (80)          | 2 (1)                |       |
| Other                             | 14.4 (97)     | 14.2 (88)          | 17.7 (9)             |       |
| Immunocompromised state           |               |                    |                      | 0.003 |
| Sepsis                            | 20.1 (135)    | 17.6 (109)         | 50.1 (26)            | < 0.0001 |
| Extracorporeal membrane oxygenation | 1.9 (13)   | 1.1 (7)            | 11.8 (6)             | < 0.0001 |
| Pediatric Risk of Mortality III   | 8 (4–12)      | 7 (3–11)           | 17 (12–30)           | < 0.0001 |
| Ventilator-free days in 28        | 23 (18–26)    | 23 (19–26)         | 20 (9–23)            | < 0.0001 |
| Length of stay in days            | 14.9 (6.9–25.6)| 14.9 (7.2–25.3) | 12.7 (5.5–27.5)     | 0.9   |
| FOMV days                         | 0 (0–3)       | 0 (0–2)            | 2 (0–5)              | 0.001 |
| % of ventilator days that are FOMV days | 0 (0–42) | 0 (0–38)          | 25 (0–70)            | 0.003 |
| Peak fluid balance, %            | 8 (3–14.5)    | 8 (3–14)           | 14 (8–24)            | < 0.0001 |
| Fluid balance on day 3, %         | 4 (0–10)      | 4 (0–10)           | 7 (0–18)             | 0.006 |
| Fluid balance on day 7, %         | 3 (–1 to 8)   | 3 (–1 to 8)        | 5.5 (0–14)           | 0.1   |

FOMV = fluid overload mechanically ventilated.

Variables are reported as % (n) for dichotomous variables and median (interquartile range) for continuous variables.
Each FOMV day represents an exposure to a large positive fluid balance in a patient who is at risk for detrimental impact from the fluid balance. Importantly, FOMV is a weight-based exposure to fluid. The consistent use of weights to quantify fluid balance controls for insensible losses and is a better representation of the physiologic impact to the patient compared with an ins and outs model. FOMV is similar to other well-known exposure measures, such as central catheter days, urinary catheter days, and nephrotoxic medications which put patients at risk for the development of central catheter-associated blood stream infections, catheter-associated urinary tract infections, and nephrotoxic acute kidney injury, respectively. Future quality improvement initiatives and research studies focused on the reduction of FOMV days may help reduce the impact of a positive fluid balance in children requiring mechanical ventilation.

Our study has important limitations. First, our study is retrospective and observational and thus can only establish association and not causality. Second, the lack of clear data regarding the types of fluid exposure limits our ability to establish this metric as an interventional target until it has been further validated in a prospective and real-time fashion. Third, our study does not demonstrate how to reduce the exposure to a large fluid balance. Interventions aimed at the reduction of FOMV days would need further evaluation. Fourth, we only included observed confounders in our regression analyses, and unobserved confounding variables may impact the relationships studied. Last, patients are weighed daily on bed scales; however; there may be inconsistencies in the daily weights that may be a confound for our findings.

**CONCLUSIONS**

FOMV days is a novel exposure measure in children with acute respiratory failure associated in a dose-dependent relationship with worse clinical outcomes. This weight-based metric needs to be further validated in a prospective fashion to be used in future quality improvement initiatives and research studies. This will help to determine the efficacy of interventions aimed at reducing fluid overload exposure in high-risk critically ill children requiring mechanical ventilation.

**TABLE 2.**

| Outcomes Based on Fluid Overload Mechanically Ventilated Categories |
|---------------------------------------------------------------|
| **Ventilator-Free Days in 28**                               |
| FOMV Days | Unadjusted IRR | Adjusted IRR |
| 0 | Reference | Reference |
| 1–2 | 0.91 (0.87–0.98) | 0.90 (0.84–0.97) |
| 3–7 | 0.85 (0.79–0.91) | 0.84 (0.78–0.91) |
| > 7 | 0.55 (0.5–0.60) | 0.55 (0.5–0.60) |
| **Mortality** | | |
| FOMV Days | Unadjusted RR | Adjusted RR |
| 0 | Reference | Reference |
| 1–2 | 2.0 (0.93–4.26) | 1.85 (0.88–3.9) |
| 3–7 | 2.63 (1.34–5.14) | 1.64 (0.87–3.1) |
| > 7 | 3.12 (1.52–6.42) | 2.11 (1.04–4.3) |
| **Length of Stay, d** | | |
| FOMV Days | Unadjusted IRR | Adjusted IRR |
| 0 | Reference | Reference |
| 1–2 | 1.14 (0.94–1.4) | 1.22 (1.00–1.5) |
| 3–7 | 1.4 (1.15–1.7) | 1.42 (1.17–1.73) |
| > 7 | 2.03 (1.62–2.56) | 2.06 (1.63–2.61) |
| **Landmark Analysis: Ventilator-Free Days in 28** | | |
| FOMV days | Unadjusted IRR | Adjusted IRR |
| 0.97 (0.94–1.01) | 0.97 (0.93–1.00) |

FOMV = fluid overload mechanically ventilated IRR = incidence rate ratio.

Negative binomial regression analyses were performed for the models for ventilator-free day at 28 d and length of stay in days. Modified Poisson regression analysis with robust error variance was performed for mortality. All regression analyses were adjusted for a priori determined covariables of age, Pediatric Risk of Mortality III score, and immunocompromised state. Landmark analysis was limited to patients intubated for the first 3 d of their PICU stay, and the FOMV days possible was limited to FOMV days in the first 3 d of their PICU stay, i.e., 0–3 possible FOMV days.

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